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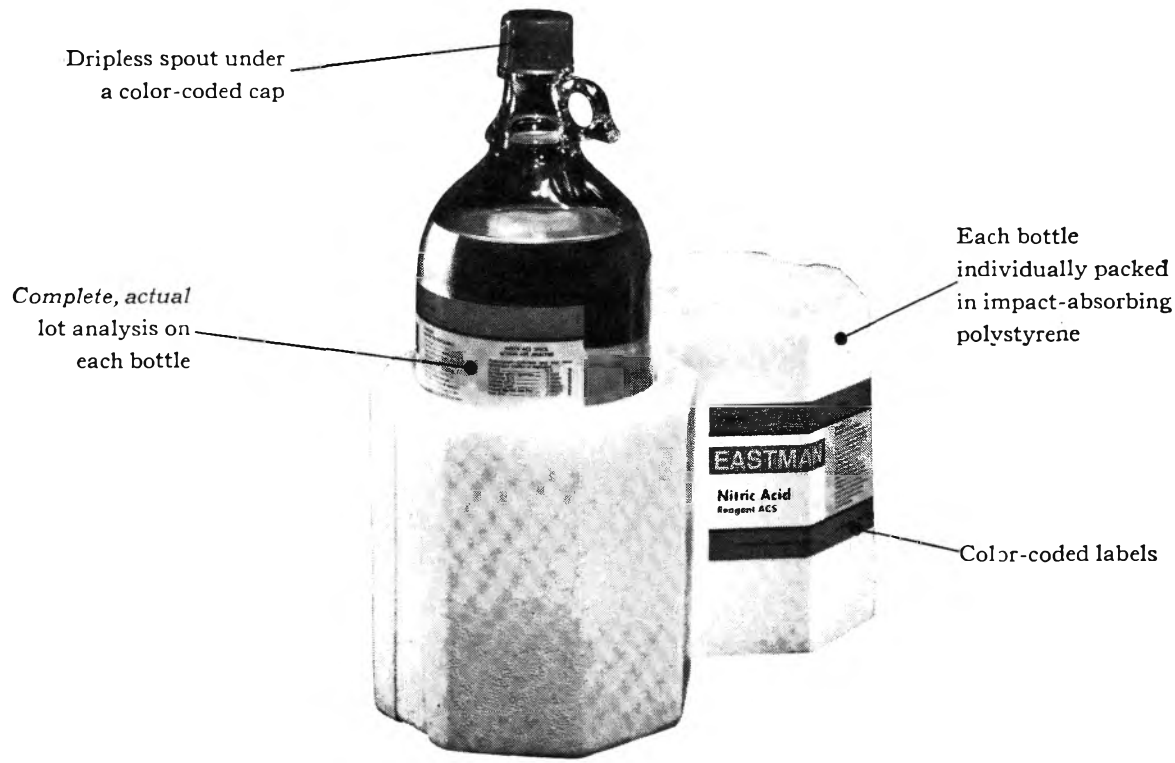

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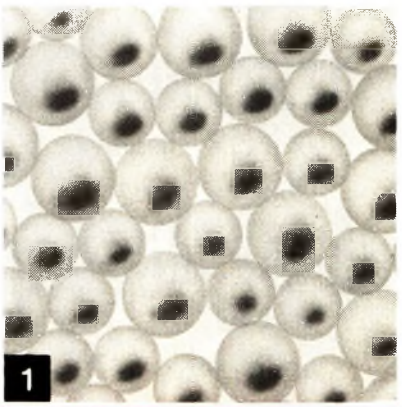

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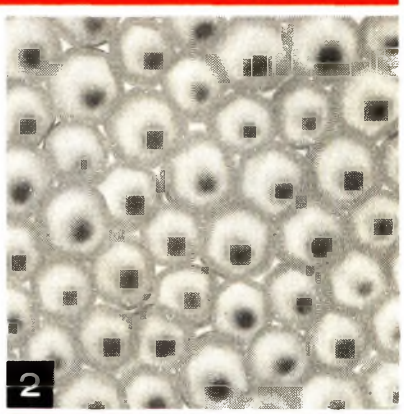

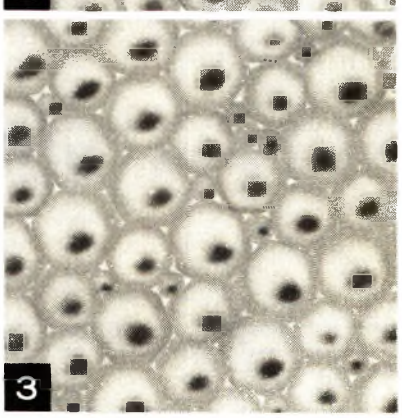

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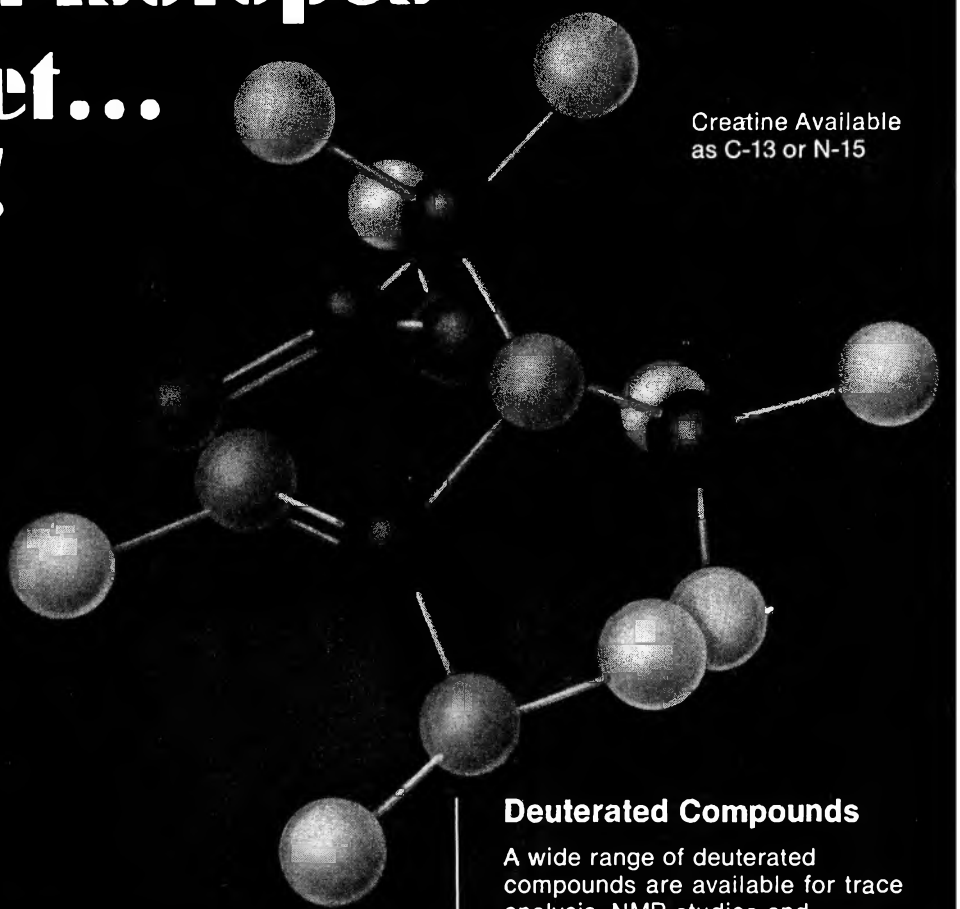

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THE CONSERVATION OF ORBITAL SYMMETRY

by R. B. WOODWARD
Department of Chemistry, Harvard University
and ROALD HOFFMANN
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The *Conservation of Orbital Symmetry* represents the first complete account, by the originators of the concept, of one of the most significant advances in theoretical organic chemistry in this century. With the aid of qualitative but powerful and incisive quantum mechanical arguments, the authors show the necessity to maintain bonding in the course of any primary reaction requires congruence between the orbital symmetry characteristics of reactants and products. The detailed stereochemical course of cycloadditions, electrocyclic reactions and sigmatropic reactions follows from such orbital symmetry considerations.

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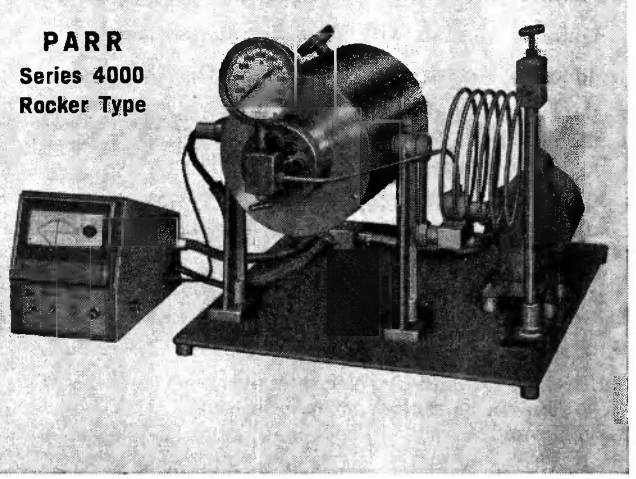

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AUTHOR INDEX

REYNOLD C. FUSON

June 1, 1970, is the 75th birthday of Reynold C. Fuson. Over 300 scientific publications dealing with such subjects as vinylogy, hindered carbonyl compounds, stable enediols, stable vinyl alcohols, and aromatic nucleophilic substitution reactions attest to his knack of finding unexpected reactions and relating them within a rational system. Four textbooks, designed for particular needs, record his devotion to instruction in organic chemistry. The high esteem of his fellow scientists is shown by many honors and responsibilities, such as membership in the National Academy of Sciences, the Nichols Medal, honorary degrees from the Universities of Illinois and Montana, the Manufacturing Chemists Association College Chemistry Teachers Award, the University of Minnesota Achievement Award, the John R. Kuebler Award of Alpha Chi Sigma, membership on the Editorial Board of Organic Syntheses, and Associate Editorship of the Journal of the American Chemical Society.

For this tribute we wish to stress two aspects of his career for which no formal awards exist and which demonstrate that he is interested in chemists as well as in chemistry.

One is the unique relationship he has had with those who studied with him. He supervised the research of 14 postdoctoral fellows, 154 Ph.D. candidates, 37 M.S. candidates, and 71 seniors and he taught thousands of others by lectures and by personal contact. While he did all that an excellent research director and a polished lecturer could do, he did more than that; he was the mentor of his students during and after their studies with him. The loyalty, respect, and affection of his students continue throughout their careers.

The other is the gratitude and admiration of those who, while they did not do research with him, have learned from him from conversations, from his writings, and from his example.

It is a small expression of great appreciation when we say

Happy Birthday to Reynold C. Fuson

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JUNE 1970

Negatively Substituted Acetylenes. III.[1] Reverse Wittig Reactions with Triphenylphosphine Oxide and Triphenylarsine Oxide

ENGELBERT CIGANEK

Contribution No. 1635 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

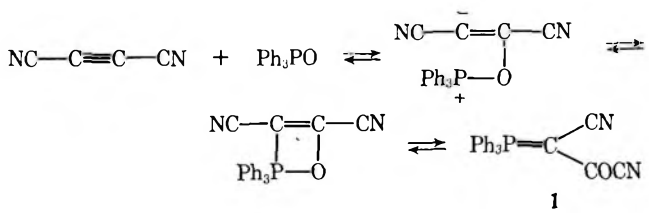
Received November 5, 1969

Dicyanoacetylene reacts with triphenylphosphine oxide in a reverse Wittig reaction to give triphenylphosphoranylideneoxalacetonitrile (1). The reaction is reversible. The analogous reaction with triphenylarsine oxide proceeds much more readily and is not, as in the case of the phosphine oxide, limited to dicyanoacetylene. Adducts of triphenylarsine oxide with methyl propiolate, dimethyl acetylenedicarboxylate, ethyl phenylpropiolate, and hexafluoro-2-butyne have been obtained.

One of the driving forces of the Wittig reaction[2] is the formation of the highly stable phosphorus–oxygen bond.[3] Consequently, reverse Wittig reactions where a P–O bond is broken are rare.[4] We have investigated the reaction of some highly electrophilic acetylenes with triphenylphosphine oxide as well as with triphenylarsine oxide to determine whether reverse Wittig reactions might be observable in these systems. An analogy was available in the reaction of activated acetylenes[5] and benzyne[6] with dimethyl sulfoxide. On the other hand, pyrolysis of a number of acylphosphoranes has been shown to give triphenylphosphine oxide and acetylenes by an intramolecular Wittig reaction.[7]

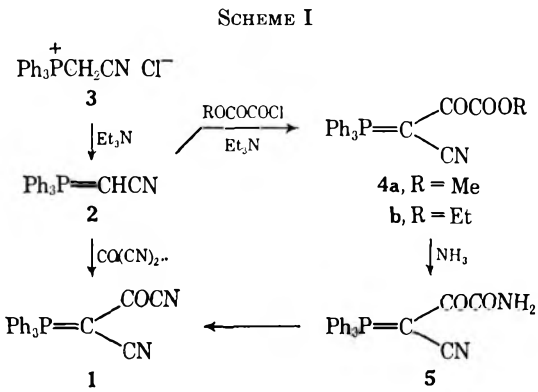
Results and Discussion

Dicyanoacetylene reacted with triphenylphosphine oxide in benzene at 160° to give triphenylphosphoranylideneoxalacetonitrile (1) in 78% yield. The structure of 1 was ascertained by an unambiguous synthesis



1

SCHEME I



(Scheme I). Acylation of triphenylphosphoranylideneacetonitrile (2) with methyl or ethyl chloroglyoxylate in the presence of triethylamine gave the triphenylphosphoranylidenecyanopyruvates (4). Cyanomethyltriphenylphosphonium chloride (3) could be used in place of 2, the latter presumably being formed first by the action of excess triethylamine. Reaction of 4b with ammonia gave the amide 5, which on dehydration furnished triphenylphosphoranylideneoxalacetonitrile (1). This phosphorane was also obtained, in low yield, by direct cyanoacylation of 2 with carbonyl cyanide.[8]

(1) E. Ciganek, *J. Org. Chem.*, **34**, 1923 (1969).

(2) A. Maercker, *Org. React.*, **14**, 270 (1965); A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966.

(3) The dissociation energy of the P–O bond is 130–140 kcal/mol: S. B. Hartley, W. S. Holmes, J. K. Jacques, M. F. Mole, and J. C. McCoubrey, *Quart. Rev. Chem. Soc.*, **17**, 204 (1963).

(4) One such example is the reaction of certain phospholene 1-oxides with isocyanates: T. W. Campbell, J. J. Monagle, and V. S. Foldi, *J. Amer. Chem. Soc.*, **84**, 3673 (1962); J. J. Monagle, T. W. Campbell, and H. F. McShane, Jr., *ibid.*, **84**, 4288 (1962); J. J. Monagle, *J. Org. Chem.*, **27**, 3851 (1962).

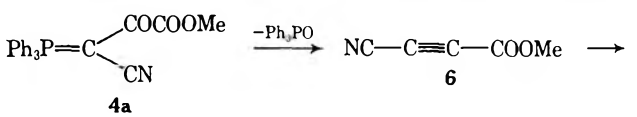
(5) E. Winterfeld, *Chem. Ber.*, **98**, 1518 (1965); E. Winterfeld and H. J. Dillinger, *ibid.*, **99**, 1558 (1966).

(6) R. Kise, T. Asari, N. Furukawa, and S. Oae, *Chem. Ind.* (London), 276 (1967); H. H. Szmant and S. Vazquez, *ibid.*, 1000 (1967); R. Gompper, E. Kutter, and G. Seybold, *Chem. Ber.*, **101**, 2340 (1968).

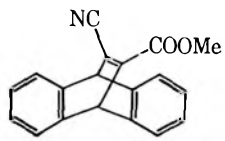
(7) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 3874 (1959); S. T. D. Gough and S. Trippett, *Proc. Chem. Soc.* (London), 302 (1961); G. Märkl, *Chem. Ber.*, **94**, 3005 (1961); R. Filler and E. W. Heffern, *J. Org. Chem.*, **32**, 3249 (1967).

(8) Carbonyl cyanide frequently reacts like an acid halide; for a review see E. Ciganek, W. J. Linn, and O. W. Webster, "Chemistry of the Cyano Group," Z. Rappoport, Ed., Interscience Publishers, London, 1970, Chapter 9.

Acylation of phosphoranes with alkyl chloroglyoxylates does not appear to have been reported before. Although we have demonstrated such an acylation with only two phosphoranes (2 and ethyl triphenylphosphoranylideneacetate), it probably is a generally applicable reaction. The phosphoranes **1**, **4**, and **5** are "resonance-stabilized" ylides[2] and thus are stable to oxygen and water at room temperature; **1** could not be alkylated with methyl iodide at 160°, nor did it react with benzaldehyde at that temperature. On pyrolysis at 300°, the phosphorane **1** reverted to triphenylphosphine oxide and dicyanoacetylene; the latter was isolated in 40% yield. Under analogous conditions, the phosphorane **4a** gave methyl cyanopropiolate (**6**) in very low yield in addition to methanol



4a **6**

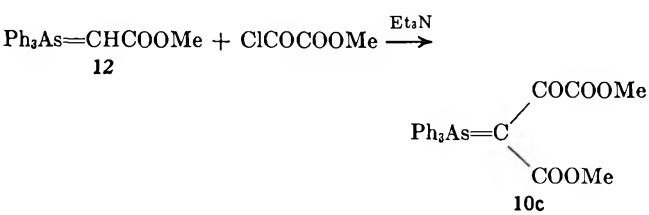


7

and other unidentified products. The ester **6** was identified by its spectral properties and conversion to the anthracene adduct **7**. These reactions are further examples of the formation of acetylenes by pyrolysis of acylphosphoranes.[7]

The reaction with triphenylphosphine oxide could not be extended to other negatively substituted acetylenes. Thus, no adducts of type **1** could be obtained on treating triphenylphosphine oxide with hexafluoro-2-butyne (160°), cyanoacetylene (160°), and dimethyl acetylenedicarboxylate (120 and 200°). Generation of benzyne in the presence of triphenylphosphine oxide similarly failed to give a 1:1 adduct. However, when triphenylarsine oxide was used instead of the phosphine oxide, methyl propiolate, ethyl phenylpropiolate, dimethyl acetylenedicarboxylate, and hexafluoro-2-butyne, as well as dicyanoacetylene, reacted readily to give the arsenic analogs **10** (Scheme II). The reaction temperatures required ranged from −70° in the case of dicyanoacetylene to +130° in the case of ethyl phenylpropiolate.

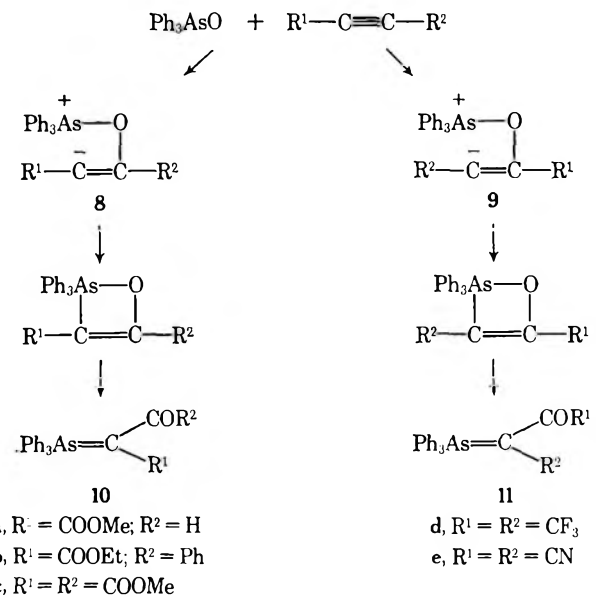
The structure of the dimethyl acetylenedicarboxylate adduct **10c** was proved by independent synthesis from methoxycarbonylmethylenetriphenylarsenic (**12**) and



12 **10c**

methyl chloroglyoxylate. In principle, two isomeric arsenic ylides could be formed in reactions involving unsymmetrically substituted acetylenes. With both methyl propiolate and ethyl phenylpropiolate, one isomer was formed to the virtual exclusion of the other. The structures of the adducts **10a** and **10b** were assigned on the basis of spectral evidence. The methyl propiolate adduct **10a** shows a one-proton singlet at τ 0.16 due to the aldehyde proton (R^2); the corresponding proton (R^2) in **11a** should absorb at considerably higher field.[9] Furthermore, the infrared spectrum of **10a** shows no band at 1740 cm^{-1}, characteristic of an alkoxycarbonyl group in α position to a keto function. This band is present in **10c** as well as in the related phosphoranes **4a** and **4b**. The ketone band in the ylides **10** occurred at 1530–1600 cm^{-1}, depending on the substituents. In the infrared spectrum of the ethyl phenylpropiolate adduct **10b**, the band at 1740 cm^{-1} again is absent. The observed selectivity is readily rationalized on the basis of the mechanism shown in Scheme II. The alkoxycarbonyl group in the initially formed zwitterion **8** provides better stabilization for the negative charge than does hydrogen and phenyl, respectively, in the alternate intermediate **9**.

SCHEME II

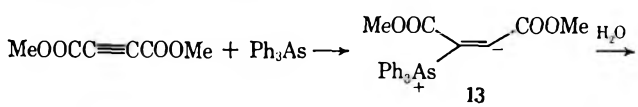


10 **11**

a, R^1 = COOMe; R^2 = H
b, R^1 = COOEt; R^2 = Ph
c, R^1 = R^2 = COOMe
d, R^1 = R^2 = CF_3
e, R^1 = R^2 = CN

Only triphenylarsine (42% yield) was isolated from the reaction of triphenylarsine oxide with cyanoacetylene at 60°. Similarly, no adduct could be isolated when benzyne was generated in the presence of triphenylarsine oxide.

The ylide **10c**, in addition to dimethyl fumarate, has previously been obtained from the reaction of triphenylarsine with dimethyl acetylenedicarboxylate,[10] and a mechanism involving fragmentation of an intermediate 1:2 adduct was proposed. In view of our results it is likely that **10c** arose instead from reaction of the diester with triphenylarsine oxide, the latter having been formed by hydrolysis of the 1:1 adduct **13**. The presence of water was reported[10] to be essential for the success of the reaction.



13

The observation that triphenylarsine oxide reacts much more readily with activated acetylenes than does

(9) The singlet due to the methylene proton in methoxycarbonylmethylenetriphenylarsenic (**12**) occurs at τ 6.8 (in $CDCl_3$).

(10) J. B. Hendrickson, R. E. Spenger, and J. J. Sims, *Tetrahedron*, **19**, 707 (1963).

its phosphorus analog is probably a consequence of the lower bond dissociation energy of the arsenic–oxygen bond[11] compared with that of the phosphorus–oxygen bond, although the relative stabilities of the phosphorus ylides **1** and **4** and of their arsenic analogs **10** may also play a part. A pertinent observation is that triphenylarsine oxide transfers its oxygen to triphenylphosphine.[12] On the other hand, no reaction occurred

$$Ph_3AsO + Ph_3P \xrightarrow[CH_2Cl_2]{105^\circ} Ph_3As + Ph_3PO$$

between triphenylphosphine and the arsenic ylide **10e** at 110°, nor between triphenylarsine oxide and the phosphorus ylide **1** under similar conditions.

Triphenylstibine oxide reacted at room temperature with dicyanoacetylene, but no pure products could be isolated. Reaction with methyl propiolate at 115° gave methyl phenylpropiolate in 40% yield; the other products were not identified. Elucidation of the mechanism of this curious phenyl transfer reaction awaits further study.

Experimental Section

Triphenylphosphoranylideneoxalacetonitrile (1) **from Dicyanoacetylene and Triphenylphosphine Oxide.**—A mixture of 5.73 g (20.6 mmol) of triphenylphosphine oxide, 1.974 g (20.6 mmol) of dicyanoacetylene,[13] and 30 ml of benzene, contained in a sealed Carius tube, was heated to 160° for 12 hr. The product was passed through 120 g of Florisil. Elution with 1000 ml of methylene chloride–tetrahydrofuran (98:2) gave 6.09 g of yellow crystals which on crystallization from 30 ml of acetonitrile gave 4.69 g of triphenylphosphoranylideneoxalacetonitrile (1) as yellow crystals, mp 222–223°. Removal of the solvent from the mother liquor and crystallization of the residue from 8 ml of acetonitrile gave an additional 0.97 g of product. The combined yield was 5.66 g (78%): uv max (MeCN) 300 mμ (ε 7900), 275 (7800), 268 (7400), and 225 (sh, 26,000); ir (KBr) 3070, 2190, 1600 (vs), 760 (doublet), and 690 cm^{-1}, among others.

Anal. Calcd for $C_{22}H_{15}N_2OP$: C, 74.58; H, 4.27; N, 7.90; P, 8.74. Found: C, 74.75; H, 4.22; N, 8.05; P, 8.72.

Methyl Triphenylphosphoranylidenecyanopyruvate (4a).—To a mixture of 100 g (0.30 mol) of cyanomethyltriphenylphosphonium chloride,[14] 100 g (1.00 mol) of triethylamine, and 800 ml of methylene chloride was added, with mechanical stirring, during 30 min, a solution of 37 g (0.30 mol) of methyl chloroglyoxylate,[15] the temperature was kept at −60°. The mixture was allowed to warm to 0°, ice and water were added, the layers were separated, and the organic phase was washed with water and concentrated sodium chloride solution and dried ($MgSO_4$). Removal of the solvent and crystallization of the residue from 200 ml of acetonitrile gave 69.5 g (60%) of methyl triphenylphosphoranylidenecyanopyruvate (4a), mp 210–211°, as pale yellow crystals. An analytical sample (MeCN) had mp 211–212°: uv max (MeCN) 295 mμ (sh, ε 450), 274 (7000), 268 (3700), and 222 (sh, 27,500); ir (KBr) 2200, 1740, and 1600 (vs) cm^{-1}, among others; nmr ($CDCl_3$) τ 2.2–2.6 (m, 15, Ph) and 6.2 (s, 3, COOMe).

Anal. Calcd for $C_{23}H_{18}NO_3P$: C, 71.31; H, 4.69; N, 3.62. Found: C, 70.86; H, 4.64; N, 3.70.

Ethyl Triphenylphosphoranylidenecyanopyruvate (4b).—To a stirred suspension of 25.62 g (85 mmol) of triphenylphosphoranylideneacetonitrile[16] in a mixture of 13.0 g (0.13 mol) of triethylamine and 200 ml of acetonitrile was added, at 5°, over a period of 30 min, a solution of ethyl chloroglyoxylate (Eastman White Label) in 50 ml of acetonitrile. The mixture was stirred at room temperature for 1 hr, the solvent was removed, and the residue was washed well with water and dried. Crystallization from 70 ml of acetonitrile gave 22.25 g (66%) of ethyl triphenylphosphoranylidenecyanopyruvate (4b) as pale yellow crystals. An analytical sample was prepared by recrystallization from acetonitrile. The melting point of both samples was 192° in one determination and 215–216° in a second determination. When a fairly large sample was introduced into the bath at 205°, it melted immediately and then resolidified. The infrared spectrum of the resolidified product, taken immediately, was essentially that of the product before heating, with small differences in the C–H out-of-plane vibration region: nmr ($CDCl_3$) 2.2–2.6 (m, 15), 5.67 (q, 2, J = 7 Hz), and 8.65 (t, 3, J = 7 Hz); uv max (MeCN) 300 mμ (sh, ε 3900), 274 (7000), 268 (7400), and 225 (26,000); ir (KBr) 2190, 1730, and 1590 cm^{-1}, among others.

Anal. Calcd for $C_{24}H_{20}NO_3P$: C, 71.81; H, 5.02; N, 3.49; P, 7.72. Found: C, 71.57; H, 5.15; N, 3.64; P, 7.79.

Diethyl Triphenylphosphoranylideneoxalacetate.—A solution of 5.40 g (39.6 mmol) of ethyl chloroglyoxylate (Eastman White Label) in 20 ml of acetonitrile was added to a suspension of 15.12 g (39.8 mmol) of ethyl triphenylphosphoranylideneacetate (Aldrich Chemical Co.) in 5.30 g (52.7 mmol) of triethylamine and 100 ml of acetonitrile, and the product was isolated as described for the preparation of ethyl triphenylphosphoranylidenecyanopyruvate. There was obtained 19.20 g of a viscous oil which crystallized partially on standing at room temperature for 2 days. Part of this material (18.11 g) was dissolved in 50 ml of hot ethyl acetate; the cooled solution, after being seeded with a crystal of the product, was allowed to stand at room temperature for 3 days. The crystals were collected by filtration and washed with ethyl acetate, giving 12.50 g (66% yield) of diethyl triphenylphosphoranylideneoxalacetate, mp 135–136°. An analytical sample, prepared by two recrystallizations from ethyl acetate, had mp 136.5–137°: nmr ($CDCl_3$) τ 2.1–2.7 (m, 15), 5.70 (q, 2, J = 7 Hz), 6.16 (q, 2, J = 7 Hz), 8.67 (t, 3, J = 7 Hz), and 9.23 (t, 3, J = 7 Hz); uv max (MeCN) 256 mμ (ε 11,000), and 225 (sh, 29,000).

Anal. Calcd for $C_{26}H_{25}O_5P$: C, 69.64; H, 5.62; P, 6.91. Found: C, 69.45; H, 5.65; P, 7.15.

Triphenylphosphoranylidenecyanopyruvamide (5).—In a 400-ml shaker tube were placed 10.15 g (25.3 mmol) of ethyl triphenylphosphoranylidenecyanopyruvate (4b) and 100 ml of tetrahydrofuran. Ammonia (28 g, 1.65 mol) was added, and the tube was heated to 90° for 6 hr. The solvent was removed, the residue was dissolved in 150 ml of boiling acetonitrile, and the hot solution was filtered. On cooling, 5.87 g of triphenylphosphoranylidenecyanopyruvamide (5) was obtained as tan crystals, mp 264° dec. The mother liquor, on standing for 3 days, deposited another 0.30 g of product. The combined yield was 6.17 g (66%). Two crystallizations from acetonitrile gave an almost colorless analytical sample, mp 266° dec: uv max (MeCN) 304 mμ (ε 6100), 275 (5700), 268 (5400), and 225 (sh, 28,000); ir (KBr) 3410, 3280, 3160, 2180, 1695, 1600, and 1550 cm^{-1}, among others.

Anal. Calcd for $C_{22}H_{17}N_2O_2P$: C, 70.96; H, 4.60. Found: C, 71.00; H, 4.83.

Dehydration of Triphenylphosphoranylidenecyanopyruvamide.—A mixture of 575 mg of triphenylphosphoranylidenecyanopyruvamide, 890 mg of phosphorus pentoxide, and 20 ml of acetonitrile was heated under reflux for 2 hr, cooled, and poured into 50 ml of 10% sodium bicarbonate solution. The product was extracted with methylene chloride; the extracts were washed with water and dried. Removal of the solvent and chromatography of the residue over Florisil gave 78 mg (14%) of triphenylphosphoranylideneoxalacetonitrile (1), eluted with methylene chloride–tetrahydrofuran (98:2) and identified by comparison of its infrared spectrum with that of the product obtained in the reaction of dicyanoacetylene with triphenylphosphine oxide.

Reaction of Triphenylphosphoranylideneacetonitrile with Carbonyl Cyanide.—A solution of 705 mg (8.8 mmol) of carbonyl cyanide[17] in 10 ml of acetic acid was added, over 30 min, to a solution of 2.675 g (8.9 mmol) of triphenylphosphoranylideneacetonitrile[16] in 35 ml of acetic acid. The temperature was kept below 20°. The solution was concentrated to dryness at room temperature, giving 3.52 g of a black viscous oil. Chromatography of 1.036 g of this product over 30 g of Florisil gave 35 mg

(11) F. S. Dainton, *Trans. Faraday Soc.*, **43**, 244 (1947).

(12) A carbon analog of this reaction has been observed in the interaction of methylenetrimethylarsenic with trimethylphosphine to give trimethylarsine and trimethylphosphinemethylene: H. Schmidbauer and W. Tronich, *Inorg. Chem.*, **7**, 168 (1968).

(13) E. Ciganek and C. G. Krespan, *J. Org. Chem.*, **33**, 541 (1968).

(14) G. Wittig and H. Pommer, German Patent 943,648; *Chem. Abstr.*, **52**, 16292 (1958).

(15) S. J. Rhoads and R. E. Michel, *J. Amer. Chem. Soc.*, **85**, 585 (1963).

(16) G. P. Schiemenz and H. Engelhard, *Chem. Ber.*, **94**, 578 (1961).

(17) W. J. Linn, R. E. Benson, and O. W. Webster, *J. Amer. Chem. Soc.*, **87**, 3651 (1965).

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(4% yield) of triphenylphosphoranylideneoxalacetonitrile (1), eluted with methylene chloride–tetrahydrofuran (98:2) and identified by its infrared spectrum.

Pyrolysis of Triphenylphosphoranylideneoxalacetonitrile (1).—A flask containing 943 mg of triphenylphosphoranylideneoxalacetonitrile (1) and 13 g of sand was connected to a vertical quartz tube, filled with pieces of quartz tube, 0.5 cm in diameter and 0.5 cm in length. The upper end of the tube was connected to a trap cooled with liquid nitrogen. The tube was heated to 300°. The flask was immersed in an air bath, evacuated to 0.1-mm pressure, and heated slowly, over 5.5 hr, to 280°. The trap contained 83 mg (40% yield) of dicyanoacetylene, identified by its infrared spectrum. The sublimate at the top of the column weighed 669 mg; its infrared spectrum was mostly that of triphenylphosphine oxide with additional bands due to unreacted starting material.

Pyrolysis of methyl triphenylphosphoranylidenecyanopyruvate (4a) (30 g, mixed with 30 g of sand) was carried out as described for the pyrolysis of triphenylphosphoranylideneoxalacetonitrile (above). The nmr spectrum of the contents of the liquid nitrogen trap (0.95 g) showed the presence of methanol and other compounds in addition to methyl cyanopropiolate (COOMe at τ 6.1, neat); ir (neat) 2180 and 1740 cm^{-1}, among others. A mixture of 0.68 g of the pyrolysate, 2.20 g of anthracene, and 8 ml of methylene chloride, contained in a sealed Carius tube, was heated to 110° for 6 hr. The solvent was removed from the cooled, filtered solution, and the residue (1.21 g) was chromatographed on 30 g of Florisil. Unreacted anthracene was eluted with hexane–benzene (4:1); the fraction eluted with methylene chloride was crystallized from acetonitrile to give 560 mg (3% based on methyl triphenylphosphoranylidenecyanopyruvate) of methyl 12-cyano-9,10-dihydro-9,10-ethenoanthracene-11-carboxylate, mp 229–230°, unchanged on further recrystallization: uv max (MeCN) 310 mμ (sh, 600), 228 (9400), and 213 (46,500); ir (KBr) 2220, 1710, and 1610 cm^{-1}, among others; nmr τ 2.5–3.0 (m, 8, aromatic H), 4.2 (s, 1, bridgehead), 4.6 (s, 1, bridgehead), and 6.2 (s, 3, COOMe).

Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.19; H, 4.50; N, 5.13.

Triphenylarsine Oxide.—To remove the water (present as a hydrate or crystal water) in commercial triphenylarsine oxide, a 100-g sample was heated under reflux with 500 ml of benzene under a Dean–Stark trap until no more water distilled (*ca.* 5 hr); 4 ml of water was collected. The arsine oxide initially went into solution and then precipitated out. The cooled mixture was filtered and the solid was dried at 135° (0.1 mm). The sample so prepared no longer showed any OH absorption in the infrared spectrum; in addition, bands at 1660, 870, 755, and 750 cm^{-1}, present in the original sample, had disappeared. All bands reappeared in a sample allowed to stand exposed to the atmosphere overnight.

Reaction of Triphenylarsine Oxide with Methyl Propiolate.—A mixture of 3.47 g of triphenylarsine oxide, 2.67 g of methyl propiolate (Columbia Organic Chemicals Co.), and 20 ml of ethyl acetate was heated under reflux for 65 hr. Removal of the solvent gave 5.00 g of a brown oil. It was redissolved in hot ethyl acetate, the solution was cooled, and the precipitate which formed on scratching was collected by filtration, washed with ethyl acetate, and dried to give 2.00 g (46% yield) of [(formyl)(methoxycarbonyl)methylene]triphenylarsenic (**10a**), mp 148–149°. A sample recrystallized from ethyl acetate had mp 147–148°: uv max (MeCN) 252 mμ (ϵ 13,500); ir (KBr) 2810, 2750, 1650, and 1605 cm^{-1} among others; nmr ($CDCl_3$) τ 0.16 (s, 1, CHO), 2.3–2.7 (m, 15, Ph), and 6.5 (s, 3, COOMe).

Anal. Calcd for $C_{22}H_{19}AsO_3$: C, 65.04; H, 4.72. Found: C, 65.18; H, 4.50.

The nmr spectrum of the mother liquors showed ethyl acetate, [(formyl)(methoxycarbonyl)methylene]triphenylarsenic, as well as a singlet at τ 1.8 which may have been due to [(methoxyoxalyl)-methylene]triphenylarsenic.

Reaction of Triphenylarsine Oxide with Dimethyl Acetylenedicarboxylate.—A mixture of 3.27 g of triphenylarsine oxide, 3.11 g of dimethyl acetylenedicarboxylate, 20 ml of ethyl acetate, and 7 ml of methylene chloride was heated under reflux for 5 min. The solvent was then distilled until the boiling point reached 75°. The precipitate obtained on cooling was collected by filtration, washed with ethyl acetate, and dried to give 2.95 g (62% yield) of [(methoxycarbonyl)(methoxyoxalyl) methylene]triphenylarsenic (**10c**), mp 213–214° dec (lit.[10] mp 214°), unchanged by crystallization from ethyl acetate: uv max (MeCN) 262 mμ (ϵ 10,000) and 220 (30,000); ir (KBr) 1740, 1675, and 1550 cm^{-1}, among others; nmr ($CDCl_3$) τ 2.2–2.7 (m, 15, Ph), 6.1 (s, 3, COOMe), and 6.7 (s, 3, COOMe).

Anal. Calcd for $C_{24}H_{21}AsO_5$: C, 62.08; H, 4.56. Found: C, 62.38; H, 4.63.

Preparation of [(Methoxycarbonyl)(methoxyoxalyl)methylene]-triphenylarsenic (10c) from (Methoxycarbonylmethylene)triphenylarsenic and Methyl Chloroglyoxylate.—A solution of 0.69 g of methyl chloroglyoxylate[15] in 3 ml of anhydrous acetonitrile was added over 10 min, to a stirred, cooled (ice bath) suspension of 2.00 g of (methoxycarbonylmethylene)triphenylarsenic[18] in 15 ml of acetonitrile and 4 ml of triethylamine. The mixture was stirred at room temperature for 1 hr and then concentrated to dryness. The residue was taken up in methylene chloride–water, the layers were separated, and the aqueous phase was extracted with methylene chloride. The combined organic phases were washed with water and concentrated sodium chloride solution and dried. Removal of the solvent gave 2.05 g of a tan solid. Crystallization from acetonitrile gave 1.60 g (65% yield) of [(methoxycarbonyl)(methoxyoxalyl)methylene]triphenylarsenic (**10c**), identical in melting point and infrared spectrum with the sample prepared from triphenylarsine oxide and dimethyl acetylenedicarboxylate (see above).

Reaction of Triphenylarsine Oxide with Dicyanoacetylene.—To a suspension of 2.23 g of triphenylarsine oxide in 30 ml of toluene was added, with stirring, at −70°, under nitrogen, during 15 min, a solution of 0.57 g of dicyanoacetylene[13] in 5 ml of toluene. The mixture was stirred at −70° for 4 hr and then allowed to come to room temperature overnight. The solid obtained on removal of the solvent was chromatographed on 80 g of Florisil. Elution with benzene–hexane (1:1) gave 33 mg of triphenylarsine. Elution with methylene chloride–tetrahydrofuran (9:1) gave 1.69 g of a solid which on crystallization from methyl ethyl ketone gave 1.08 g of [(cyano)(cyanocarbonyl)methylene]triphenylarsenic (**10e**), mp 216–217°. Another 0.40 g of the product, mp 216–217°, was obtained by removal of the solvent from the mother liquors and crystallization of the residue from methyl ethyl ketone: combined yield 1.48 g, 54%; uv max (MeCN) 297 mμ (ϵ 7900), 270 (6400), 264 (5900), and 220 (sh, 28,400); ir (KBr) 2190, 1590, and 1575 cm^{-1}, among others.

Anal. Calcd for $C_{22}H_{15}AsN_2O$: C, 66.34; H, 3.80; N, 7.03. Found: C, 66.34; H, 3.94; N, 7.17.

Reaction of Triphenylarsine Oxide with Ethyl Phenylpropiolate.—A mixture of 6.86 g of triphenylarsine oxide and 21.16 g of ethyl phenylpropiolate (Columbia Organic Chemicals Co.) was placed in a Carius tube which was sealed and heated to 130° for 21 hr. The excess ethyl phenylpropiolate was removed by shortpath distillation (100° bath temperature, 0.1-μ pressure). The residue was dissolved in 14 ml of hot benzene, 14 ml of cyclohexane was added, and the mixture was allowed to cool slowly. The pale yellow crystals were collected by filtration and washed with cyclohexane–benzene (1:1) to give 9.57 g of [(benzoyl)(ethoxycarbonyl)methylene]triphenylarsenic (**10b**), 90% yield), mp 118–125°. Crystallization of 9.09 g of the crude product from 16 ml of ethyl acetate gave 6.70 g of product, mp 144–145°. An analytical sample, obtained by crystallization from ethyl acetate, had mp 145–146°: uv max (MeCN) 285 (sh, ϵ 6400), 270 (7600), 265 (7700), and 220 (35,400); nmr ($CDCl_3$) τ 2.1–3.0 (m, 20, Ph), 6.3 (q, 2, CH_2), and 9.4 (t, 3, CH_3); ir (KBr) 1670 and 1530 cm^{-1}, among others.

Anal. Calcd for $C_{29}H_{25}AsO_3$: C, 70.16; H, 5.08. Found: C, 70.39; H, 5.07.

Reaction of Triphenylarsine Oxide with Hexafluoro-2-butyne.—In a Carius tube were placed 10 g of triphenylarsine oxide, 20 ml of methylene chloride, and 5 ml of hexafluoro-2-butyne (Columbia Organic Chemicals Co). The tube was sealed under vacuum and heated to 50° for 16 hr. Removal of the solvent and crystallization of the residue from 55 ml of isopropyl alcohol gave 11.18 g (75% yield) of [(trifluoromethyl)(trifluoroacetyl)-methylene]triphenylarsenic (**10d**), mp 157–159°, unchanged by crystallization from isopropyl alcohol: uv max (MeCN) 270 mμ (ϵ 6000), 263 (7200), 258 (7100), 220 (sh, 27,600); ir (KBr) 1570 cm^{-1}, among others; ^{19}F nmr, two quartets of equal intensities at +2395 and +3995 cps from external Freon-11, J = 11.5 cps.

Anal. Calcd for $C_{22}H_{15}AsF_6O$: C, 54.57; H, 3.12. Found: C, 54.86; H, 3.20.

Reaction of Triphenylphosphine with Triphenylarsine Oxide.—A mixture of 1.04 g (32.4 mmol) of triphenylarsine oxide, 0.85 g

(18) N. A. Nesmeyanov, V. V. Pravdina, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **155**, 1364 (1964).

(32.4 mmol) of triphenylphosphine, and 2 ml of anhydrous methylene chloride was placed in a Carius tube which was then sealed under nitrogen and heated to 105° for 4.5 hr (no reaction occurred at room temperature over a period of 3 weeks). The infrared spectrum of the crude product indicated the absence of triphenylarsine oxide (within detectability by this method). Chromatography over Florisil and elution with benzene gave 0.92 g (93%) of triphenylarsine, mp 60–61°, undepressed by admixture of an authentic sample; the product was also identified by its infrared spectrum. Elution with methylene chloride–tetrahydrofuran (7:3) gave 0.81 g (86%) of triphenylphosphine oxide which was identified by comparison of its infrared spectrum with that of an authentic sample. Elution with tetrahydrofuran–methanol (9:1) gave 0.05 g of triphenylarsine oxide hydrate as indicated by its infrared spectrum.

Registry No.—Triphenylphosphine oxide, 791-28-6; triphenylarsine oxide, 1153-05-5; **1**, 23853-23-8; **4a**, 23853-24-9; **4b**, 23853-25-0; **5**, 23853-26-1; **10a**, 23853-27-2; **10b**, 23853-28-3; **10c**, 23853-29-4; **10d**, 23853-30-7; **10e**, 23853-31-8; methyl 12-cyano-9,10-dihydro-9,10-ethenoanthracene-11-carboxylate, 23853-32-9.

Adducts of Acetylenes and Sulfur Dichloride

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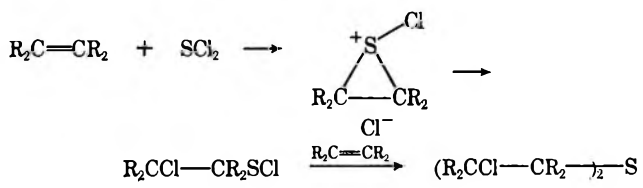
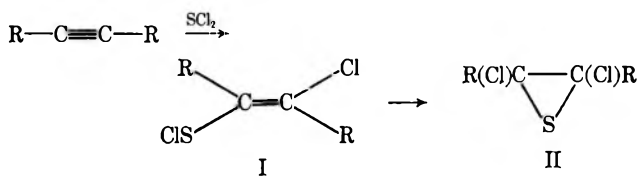
Reactions of selected acetylenes with sulfur dichloride have been studied. Dialkylacetylenes afford the corresponding divinyl sulfides (III) in quantitative yield. Diphenylacetylene provides either 3-chloro-2-phenylbenzo[*b*]thiophene (IV) or the divinyl sulfide VIII, depending upon the reaction conditions. In certain cases it is possible to isolate in good yield the intermediate vinylsulfenyl chloride, which can be utilized in a variety of synthetic schemes. The stereochemistry of the acetylene adducts is *trans*. Orientation of addition to unsymmetrical acetylenes is largely anti-Markovnikov. This orientation has been found to be relatively insensitive to the nature of the solvent. The relative reactivity of sulfur dichloride to olefins and acetylenes follows the usual order of electrophiles except with *trans*-stilbene, which was always the least reactive member in competition experiments.

Interest in the organic chemistry of sulfur dichloride has recently been revived and has led to the syntheses of a number of novel sulfur-containing heterocycles.[1-5] However, the investigations of interactions with multiple bonds to date have been largely limited to reactions of sulfur dichloride and olefins. Surprisingly, no report of a reaction of sulfur dichloride with an acetylene has appeared in the literature. We present here the results of the addition of this versatile reagent to diaryl-, arylalkyl-, and dialkylacetylenes.

From the products (and most importantly their stereochemistry) resulting from reaction of sulfur dichloride and olefinic systems, it has been concluded[1-5] that the mechanistic course of this reaction is the initial formation of an episulfonium ion, which is then opened to an alkylsulfenyl chloride. This latter species may then proceed to products by reaction with another olefinic bond.

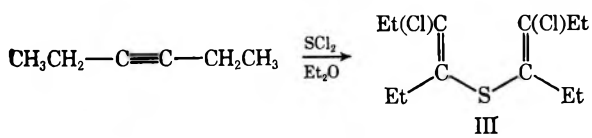


The analogous reaction with alkynes is more difficult to predict, especially in view of the uncertainty of the stereochemistry of electrophilic addition to triply bonded species.[6] However, it has been shown by a number of workers that the addition of sulfenyl halides to alkynes proceeds so as to afford *trans* products almost exclusively.[7-9] Initially it was hoped by us that the final product of this reaction would be a thiirane, thus providing a simple route to this sometimes elusive ring system. By analogy to the reactions of sulfur dichloride with olefins and the reactions of other electrophiles, such as bromine, with acetylenes the initial adduct would be expected to be a vinylsulfenyl chloride (I). Ring closure resulting from internal attack of the sulfenyl chloride upon the adjacent double bond could then provide the thiirane (II).



Results and Discussion

The first acetylene examined in our study was the readily available 3-hexyne. Addition of freshly distilled sulfur dichloride to an ethereal solution of 3-hexyne afforded the divinyl sulfide (III) as a colorless

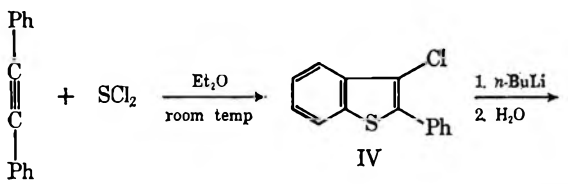


liquid in 95% yield. The structure assigned was founded on the mass spectrum (base and parent peak *m/e* 266), elemental analysis, the nmr spectrum (showing only two nonequivalent ethyl groups), and conversion

(1) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).
(2) E. D. Weil, K. J. Smith, and R. J. Gruber, *ibid.*, **31**, 1669 (1966).
(3) F. Lautenschlaeger, *ibid.*, **31**, 1679 (1966).
(4) F. Lautenschlaeger, *Can. J. Chem.*, **44**, 2813 (1966).
(5) F. Lautenschlaeger, *J. Org. Chem.*, **33**, 2620, 2627 (1968).
(6) T. C. Fahey and D. J. Lee, *J. Amer. Chem. Soc.*, **88**, 5555 (1966), and references cited therein.
(7) A. Dondoni, G. Modena, and G. Scorrano, *Boll. Sci. Fac. Chim. Ind. Bologna*, **22**, 26 (1964).
(8) V. Caló, G. Melloni, G. Modena, and G. Scorrano, *Tetrahedron Lett.*, No. 49, 4399 (1965).
(9) L. DiNunno, G. Gelloni, G. Modena, and G. Scorrano, *ibid.*, No. 49, 4405 (1965).

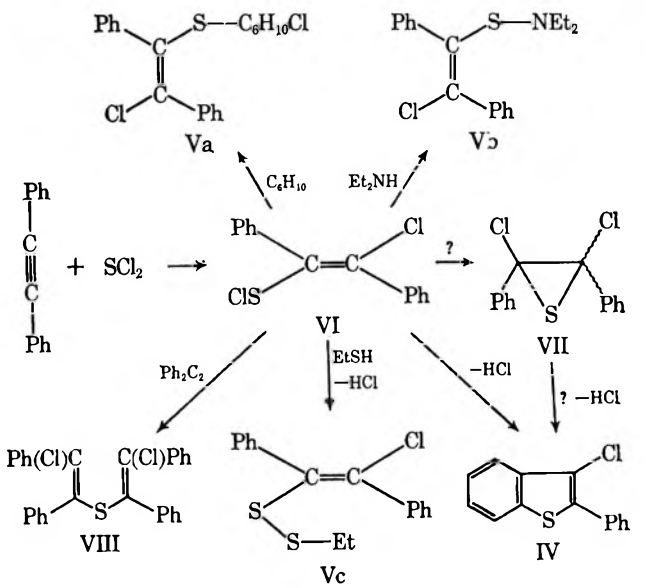
of the corresponding sulfone into propionic acid *via* ozonolysis. Inversion of the addition procedure, changes in dilution factors, and temperature changes failed to affect the nature or yield of product. No evidence of the presence of a dichlorothiirane could be found.

A dramatically different result was obtained when this reaction was attempted with a diarylacetylene. Dropwise addition of an equimolar solution of sulfur dichloride in dry ether to an ether solution of diphenylacetylene at room temperature led to isolation of a bright yellow solid after solvent removal *in vacuo*. Upon standing at room temperature this material lost most of its color, with concomitant hydrogen chloride loss, to provide a white solid (IV). This same conversion could be quantitatively performed by washing a methylene chloride solution of the product with aqueous sodium bicarbonate. Owing to the extreme instability of the initial product, spectral observations were always made on mixtures; however, the mass spectrum clearly showed that it was a 1:1 adduct of diphenylacetylene and sulfur dichloride which lost the elements of SCl_2 in stepwise processes to return to diphenylacetylene. The structure of the ultimate, colorless product was assigned as 3-chloro-2-phenylbenzo[*b*]thiophene (IV) on the basis of melting point (lit.[10] mp 67–68°), mass spectrum (parent ion *m/e* 244 with proper isotopic ratios for SCl), elemental analysis, and conversion into the known 2-phenylbenzo[*b*]thiophene[11] by dechlorination with *n*-butyllithium. 3-Chloro-2-phenylbenzo[*b*]thiophene (IV) was obtained from diphenylacetylene in this manner in yields up to 90%.

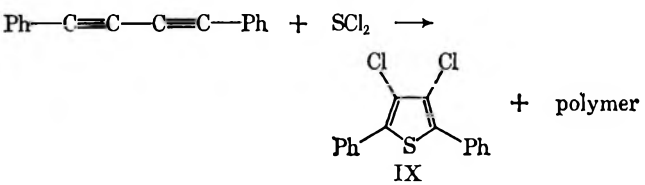


One question with which we were confronted at this point was whether IV arose from initial formation of the vinylsulfenyl chloride VI followed by electrophilic attack by sulfur on the adjacent aromatic ring or whether it was a thermolysis product of the diphenyldichlorothiirane VII. Certainly the latter-named process would appear an unnecessary consideration except that analogy for the conversion of VII into IV is found in the known thermal conversions of several α-chloroepisulfides to benzo[*b*]thiophenes by both Staudinger[12] and Schönberg.[13]

Evidence that VI was the intermediate with which we were dealing was easily obtained. A number of derivatives of VI were prepared through reaction with mercaptans, secondary amines, and olefins, thus further confirming its structure. The synthetic possibilities of being able to stop this reaction at the 1:1 adduct stage are therefore numerous and quite attractive. When the sulfur dichloride–diphenylacetylene reaction was run as before, but with methylene chloride as the solvent, no IV was obtained but high yields of the divinyl sulfide VIII were afforded. Compound VIII was also the sole product when 2 equiv of diphenylacetylene were employed. It was at first presumed that this product change in going to methylene chloride must be solely due to a change in solvent polarity; however, when the reaction was accomplished in either hexane or acetonitrile, the divinyl sulfide VIII was again the only product isolated. While the unique role of ether is not presently understood, it is true that by varying the reaction conditions either product, and mixtures of the two, may be obtained from all of these solvents. Presumably, ether solvates and stabilizes in some fashion the intermediate sulfenyl chloride so as to make the intermolecular process less favorable.



Another illustration of the synthetic utility of the sulfur dichloride–acetylene system is the reaction with diphenylbutadiyne, which yields 3,4-dichloro-2,5-diphenylthiophene (IX), albeit in low yield.



Concerning the mode of addition of sulfur dichloride to alkynes, one must first consider similar work which has been reported for alkyl- and arylsulfenyl chlorides. First, although the investigations of Fahey[6] have shown that addition of protonic acids to alkynes may proceed either in a *cis* or *trans* fashion, additions of sulfenyl chlorides have been found to proceed solely or almost exclusively in a *trans* fashion.[7,8,14–16] It might be assumed that in the case of arylacetylenes the reaction would proceed in a Markovnikov fashion, but the orientation has been found to be highly solvent de-

(10) E. J. Geering, U. S. Patent 3,278,552 (1966).

(11) M. G. Voronkov and V. Udre, *Khim. Geterotsikl. Soedin.*, **4**, 527 (1966); *Chem. Abstr.*, **66**, 65344 (1967). G. M. Badger, N. Kowanko, and W. H. F. Sasse, *J. Chem. Soc.*, 2969 (1960).

(12) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 840 (1920).

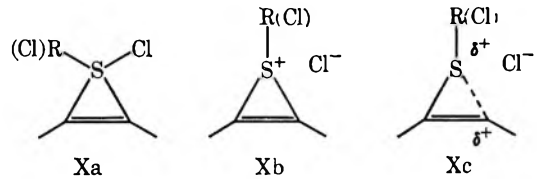
(13) A. Schönberg and L. Varga. *Ann. Chem.*, **483**, 176 (1930).

(14) V. Caló, G. Modena, and G. Scorrano, *J. Chem. Soc., C*, 1339 (1968).

(15) C. H. Schmidt and M. Heinola, *Quart. Rep. Sulfur Chem.*, **2**, 311 (1967).

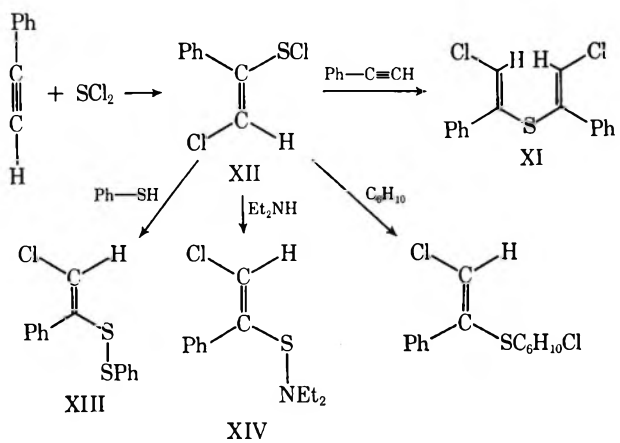
(16) V. Caló, G. Scorrano, and G. Modena, *J. Org. Chem.*, **34**, 2020 (1969).

pendent. A strong preference for Markovnikov orientation is observed only in highly polar solvents (*e.g.*, acetic acid) while less polar solvents (*e.g.*, ethyl acetate) afford mainly anti-Markovnikov products. Such results are most easily explained by the assumption of an initial complex which may be either covalent (Xa) or ion paired (Xb). The nature of this intermediate would depend upon the ion-stabilizing characteristics of the solvent. With a single electron-donating substituent on the reacting acetylene and an ionizing solvent, the intermediate could take on much of the character of Xc. Therefore the observation of a predominance of anti-Markovnikov products in solvents of low polarity can be simply explained on the basis of steric crowding in the transition state for nucleophilic attack by chloride ion. Similar conclusions have been recently reached by Modena.[16]



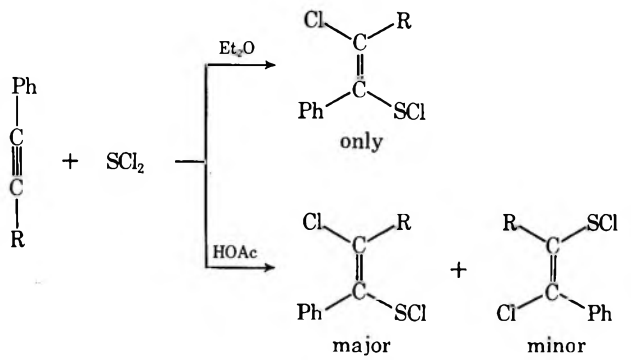
Xa Xb Xc

With diphenylacetylene the addition of sulfur dichloride is occurring in a *trans* fashion, since the resulting vinylsulfenyl chloride is able to cyclize to a benzo[*b*]thiophene. To obtain situations where there would be a possibility for both Markovnikov and anti-Markovnikov addition, two unsymmetrical acetylenes were studied. Reaction of 2 equiv of phenylacetylene with sulfur dichloride in ether or methylene chloride provided the divinyl sulfide XI, while equimolar amounts yielded the vinylsulfenyl chloride XII. The latter material was remarkably stable and could be purified by distillation. Derivatives of XII were prepared through reaction with olefins, secondary amines, and mercaptans.



The stereochemistry of XII is assumed to be *trans* as is the case with diphenylacetylene. If the addition had taken place in a Markovnikov fashion the resulting sulfenyl halide would be expected to form 3-chlorobenzo[*b*]thiophene but this product was not observed. Changing the solvent to acetic acid would be expected to provide a considerable amount of the Markovnikov product and ultimately the benzo[*b*]thiophene. The results were much less dramatic than expected and a maximum yield of *ca.* 16% 3-chlorobenzo[*b*]thiophene (determined from the nmr spectrum of the crude reaction mixture) could be obtained.

Similar results were found for 1-phenylpropyne. In solvents of low polarity, the vinylsulfenyl chloride was produced with only minor contamination by the divinyl sulfide when equimolar amounts of the two reactants were employed. Use of acetic acid as the solvent medium provided no more than 20% of the benzo[*b*]-thiophene product. It is therefore quite clear that steric effects on the nucleophilic addition of chloride anion play the largest role regardless of the solvent nature. This situation has been most conclusively established in the case of sulfenyl halide addition to olefins.[17]



(R = H, CH_3)

An interesting feature of the reaction of sulfur dichloride with acetylenes to afford divinylacetylenes is that both sulfur dichloride and the vinylsulfenyl chloride prefer to attack an acetylene molecule rather than either another vinylsulfenyl chloride or the product divinyl sulfide. It has been conclusively shown that olefins are more reactive to sulfenyl halides than are alkynes.[18] Even with strongly electron-withdrawing groups attached to the sulfenyl chloride there is still a significant difference in the reaction rates of these two multiple bonds. Presumably our observations on olefin–acetylene reactivity result from the decreased π-electron density of the olefin products which are substituted with electronegative groups. In a qualitative fashion we set out to check this assumption through a series of competition experiments. When 0.5 equiv of sulfur dichloride was slowly added to an equimolar solution of cyclohexene and diphenylacetylene, immediate examination of the resulting mixture by nmr revealed that the products were almost exclusively those derived from cyclohexene. However, when a similar competition was performed between the more comparable *trans*-stilbene and diphenylacetylene, only products derived from diphenylacetylene were afforded. This latter result was totally unexpected, especially in view of the observations by Kharasch[18] that stilbene was more reactive to 2,4-dinitrobenzenesulfenyl chloride than was diphenylacetylene and by Robertson[19] that stilbene was some 250 times more reactive toward bromine than was diphenylacetylene. Similar results were obtained when phenylacetylene replaced diphenylacetylene in these experiments. To determine the role of the aryl groups, the same competitions were examined

(17) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **90**, 2075 (1968).
(18) N. Kharasch and C. N. Yiannios, *J. Org. Chem.*, **29**, 1190 (1964).
(19) P. W. Robertson, W. E. Dasent, R. M. Milburn, and W. H. Oliver, *J. Chem. Soc.*, 1628 (1950).

with 2-butyne as the acetylenic member. All olefins examined in our laboratory to date have proved to be considerably more reactive to SCl_2 than the acetylenes employed with the glaring and consistent exception of *trans*-stilbene. The factors involved in this inconsistency are presently under active investigation in our laboratory.

Experimental Section

Melting points and boiling points are uncorrected. Microanalyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany. The nmr spectra were recorded on a Varian A-60 instrument; chemical shifts are measured in parts per million downfield from tetramethylsilane. The mass spectra were measured with a Atlas CH-4 mass spectrometer. Commercial sulfur dichloride (Matheson Coleman and Bell) was purified by vacuum distillation to remove chlorine, followed by two distillations at atmospheric pressure using equipment previously washed with a dilute solution of PCl_3 in methylene chloride.

Bis-4-chlorohex-3-en-2-yl Sulfide (III).—To a stirred solution of 8.21 g (0.10 mol) of 3-hexyne in 15 ml of dry ether was added dropwise a solution of 6.18 g (0.06 mol) of freshly distilled sulfur dichloride in 5 ml of dry ether. The temperature of the reaction was maintained at 0° and the addition required 45 min. Evaporation of the solvent and distillation of the liquid residue gave 12.7 g of a yellow liquid, bp 75–95° (0.3 mm). Redistillation using a Vigreux column afforded 12.30 g (92%) of colorless III: bp 92–93° (1.1 mm); the nmr spectrum showed only two nonequivalent ethyl groups; mass spectrum *m/e* 268 (69% of 266 peak, therefore the p + 2 peak for the parent ion containing SCl_2), 266 (p), 231 (p − Cl), 149 (p − $C_6H_{10}Cl$, S–C cleavage), and 115 (base peak).

Anal. Calcd for $C_{12}H_{20}Cl_2S$: C, 53.93; H, 7.54; S, 12.00. Found: C, 54.27; H, 7.58; S, 12.17.

3-Chloro-2-phenylbenzo[*b*]thiophene (IV).—A solution of 1.03 g (0.01 mol) of sulfur dichloride in 10 ml of dry ether was added dropwise at room temperature to a stirred solution of 1.78 g (0.01 mol) of diphenylacetylene in 20 ml of dry ether. Solvent removal *in vacuo* afforded a bright yellow, crystalline solid which readily lost hydrogen chloride to give near quantitative yields of IV. Conversion into IV was also accomplished by dissolving 0.3 g of the yellow solid VI in 15 ml of methylene chloride and washing with 25 ml of 2% sodium bicarbonate solution in a separatory funnel. The aqueous layer was separated and extracted twice with 20 ml of methylene chloride. The combined methylene chloride solutions were dried over magnesium sulfate and the solvent was evaporated to afford an oily residue. Crystallization from methanol gave 0.19 g (75%) of white, crystalline IV: mp 67° (lit.[10] mp 66–67°); mass spectrum *m/e* 246 (38% of 246 peak, therefore the p + 2 peak for the parent ion containing SCl), 244 (parent ion and base peak), 208 (−HCl), 165, 122 (p^{2+}), and 104.

Anal. Calcd for $C_{14}H_9SCl$: C, 68.71; H, 3.71; S, 13.10; Cl, 14.49. Found: C, 68.32; H, 3.66; S, 12.94; Cl, 14.51.

2-Phenylbenzo[*b*]thiophene.—To a stirred solution of 1.000 g (4.1 mmol) of IV in 15 ml of dry ether under N_2 was added 0.262 g (4.1 mmol) of *n*-butyllithium. The reaction was exothermic and an orange-brown color was generated. After stirring for 15 min at room temperature and refluxing for an additional 5 min, the reaction was decomposed with dilute HCl. The aqueous layer was separated and washed with three 20-ml portions of methylene chloride. The combined organic layers were dried over magnesium sulfate. Evaporation of the solvent left a yellow, crystalline solid which was recrystallized from methylene chloride–ether to afford 0.10 g (12%) of white, crystalline 2-phenylbenzo[*b*]thiophene, mp 172–173° (lit.[11] mp 176°).

Anal. Calcd for $C_{14}H_{10}S$: C, 79.96; H, 4.79; S, 15.25. Found: C, 80.23; H, 4.71; S, 15.25.

2-Chloro-1,2-diphenylethenesulfenyl Chloride, (*E*)-VI.—A solution containing 6.00 g (33.7 mmol) of diphenylacetylene in 100 ml of dry ether was added during 1.5 hr to a stirred solution of 3.47 g (33.7 mmol) of freshly distilled sulfur dichloride in 200 ml of refluxing dry ether, and 50-ml aliquots of the resulting orange solution containing 1.58 g (5.61 mmol) of VI were used in the following procedures.

A. Cyclohexyl-2-chloro-1,2-diphenylethen-1-yl Sulfide (Va).—The 50-ml aliquot of VI was added to a solution containing a slight molar excess of cyclohexene in dry ether. After stirring for 30 min the solvents were removed *in vacuo* to afford a yellow oil. Crystallization from ether–methanol gave 1.00 g (49%) of white, crystalline Va: mp 91–92°; nmr (CCl_4) 1.59 (m, 8, methylene H), 2.57 (m, 1, HCS), 3.83 (m, 1, HCCl), and 7.40 (m, 10, ArH); mass spectrum *m/e* 362 (parent), 210 (base peak, p − $C_6H_{10}Cl$), and 178 (p − $C_6H_{10}SCl_2$).

B. Bis-2-chloro-1,2-diphenylethenyl Sulfide, (*E*)-VIII.—The 50-ml aliquot of VI was added to a solution of 1.00 g (56 mmol) of diphenylacetylene in 25 ml of ether. After stirring for 30 min the ether was evaporated to leave a pale yellow solid. Crystallization from methylene chloride–hexane gave a quantitative yield of VIII. Further recrystallization from chloroform–hexane gave colorless needles, mp 151–152°.

An alternate preparation of VIII involved addition of an equimolar amount of sulfur dichloride in methylene chloride to an ice-cooled, room temperature or refluxing solution of diphenylacetylene in methylene chloride. The conditions were the same as for the preparation of IV. However, removal of solvent *in vacuo* followed by crystallization from methanol provided a 70% yield of VIII: mp 152.0–152.5°; nmr (CCl_4) 7.33 (m); mass spectrum *m/e* 460 (68% of 458 peak, p + 2), 458 (parent ion), 423 (p − Cl), 388 (p − Cl_2), 356 (M* for 423 → 388), 210 (p − $Ph_2C_2Cl_2$), and 178 (base peak, Ph_2C_2).

Anal. Calcd for $C_{28}H_{20}SCl_2$: C, 73.20; H, 4.39; S, 6.98; Cl, 15.43. Found: C, 73.04; H, 4.28; S, 6.97; Cl, 15.66.

C. Ethyl 2-Chloro-1,2-diphenylethen-1-yl Disulfide (Vc).—The 50-ml aliquot of VI was added to a solution of excess ethyl mercaptan in 25 ml of dry ether. After stirring for 30 min the solvent was evaporated and the resulting yellow oil crystallized from ether–methanol to afford 0.037 g of white, cottonlike Vc: mp 57–58°; nmr ($CDCl_3$) 0.97 (t, 3, methyl H), 2.20 (q, 2, methylene H), and 7.43 (m, 10, ArH); mass spectrum *m/e* 306 (parent ion) and 210 (base peak, *p* − EtSCl).

D. N,N-Diethyl 2-chloro-1,2-diphenylethen-1-yl Sulfenamide (Vb).—The 50-ml aliquot of VI was added to a 25-ml ether solution containing an excess of diethylamine. After 30 min of stirring at room temperature the solution was filtered and the solvent was evaporated *in vacuo*. The resulting yellow oil was crystallized from hexane–methanol and yielded 0.50 g (28%) of white, crystalline Vb: mp 57–58°; nmr ($CDCl_3$) 0.79 (t, 6, methyl H), 2.51 (q, 4, methylene H), and 7.41 (m, 10, ArH); mass spectrum *m/e* 317 (parent ion) and 210 (base peak, p − Et_2NCl).

3,4-Dichloro-2,5-diphenylthiophene (IX).—A 10-ml solution of 1.92 g (0.01 mol) of diphenylbutadiyne and a 10-ml solution of 1.03 g (0.01 mol) of sulfur dichloride both in methylene chloride were simultaneously added over a 20-min period to 10 ml of stirred, ice-cooled methylene chloride. After stirring for an additional 2 hr at 0°, the solvent was removed from the dark solution *in vacuo*. After redissolving the dark, viscous mass in methylene chloride, it was percolated through a short column packed with neutral alumina (Woelm) in ether. Crystallization from acetone afforded 0.50 g (17%) of yellow, crystalline IX, mp 133–135°. Repeated recrystallization from acetone gave very faintly yellow crystals: mp 136–137° (lit.[20] mp 127–129°); mass spectrum *m/e* 306 (70% of 304, p + 2) and 304 (parent ion).

Anal. Calcd for $C_{16}H_{10}SCl_2$: C, 62.96; H, 3.30; S, 10.50; Cl, 23.23. Found: C, 62.93; H, 3.30; S, 10.54; Cl, 23.34.

2-Chloro-1-phenylethenesulfenyl Chloride (XII).—A solution containing 4.00 g (39.2 mmol) of phenylacetylene in 150 ml of dry methylene chloride was added over a 3-hr period to a rapidly stirred solution of 4.04 g (39.2 mmol) of sulfur dichloride in 350 ml of refluxing methylene chloride. Evaporation of the solvent left a red-orange, *foul*-smelling liquid. Analysis by nmr revealed complete loss of phenylacetylene.

Distillation gave 3.50 g (43%) of red-orange liquid collected at 74–78° (0.25 mm). It is important that the lowest possible pot temperature be maintained during this distillation to avoid excessive polymerization of the product. The mass spectrum showed no parent ion but had peaks at *m/e* 174 (65% of 172, therefore Cl_2 present), 172 (p − S), 139 (33% of 137, therefore one chlorine), 137 (p − SCl), and 105 (base peak); nmr (CCl_4) 6.79 (s, 1, olefinic H) and 7.37 (m, 5, ArH). Addition of phenylacetylene to a methylene chloride solution of XII gave XI as a

(20) C. L. Moyle and L. R. Drake, U. S. Patent 2,527,372 (1950). No other information concerning this compound is provided other than a chlorine analysis of 21.7%. We feel that their assignment of structure is at least questionable.

mixture of inseparable isomers as determined by nmr and mass spectroscopy.

Phenyl 2-Chloro-1-phenylethene Disulfide (XIII).—A solution of 0.268 g (2.44 mmol) of thiophenol in 5 ml of dry ether was added to a stirred solution of 0.50 g (2.44 mmol) of XII in 20 ml of dry ether at room temperature. After 15 min the ether was evaporated *in vacuo* to leave 0.68 g (100%) of viscous, rather unstable yellow liquid (XIII): nmr (CCl_4) 6.49 (s, 1, vinyl H) and 7.19 (m, 10, ArH). The mass spectrum showed no parent ion but proved the incorporation of thiophenol by the spectrum's base peak at 109 (PhS).

Addition of diethylamine to XII in the same fashion afforded the unstable N,N-diethylsulfenamide derivative (XIV): nmr (CCl_4) 1.06 (t, 6, methyl H), 2.80 (q, 4, methylene H), 6.30 (s, 1, olefinic H), and 7.31 (complex m, 5, ArH).

General Procedure for Competition Reactions.—A solution of 0.5 equiv of sulfur dichloride in 10 ml of dry ether was added over 15 min to a stirred solution containing 1 equiv each of alkene and alkyne in 20 ml of dry ether at 30° (molar ratio, SCl_2 to alkene to alkyne of 0.5:1:1). Stirring was continued for 0.5 hr and the solvents were evaporated. Products were immediately examined by nmr and areas were correlated to the relative amounts of the various products.

Registry No.—Sulfur dichloride, 10545-99-0; III, 23852-88-2; IV, 2326-63-8; Va, 23852-90-6; Vb, 23852-91-7; Vc, 23852-92-8; VIII, 23852-93-9; IX, 23852-94-0; XII, 23852-95-1.

Acknowledgments.—The authors are indebted to both the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health, Public Health Service (Grant GM 16689-01), for support of this work.

Stereoselectivity in the Debromination of the Stilbene Dibromides by Several Metals and Inorganic Reductants in Several Solvents[1a]

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If *meso*-stilbene dibromide is debrominated by any reductant in any solvent, the product is always 100% *trans*-stilbene. With *dl*-stilbene dibromide, the debromination results are variable: two-electron reductants such as iodide, platinum(II), benzenesulfinate, thiophenolate, and hydride yield *ca.* 75–90% *cis;* one-electron reductants, such as β-naphthol, copper(I), iron(II), chromium(II), titanium(III), etc., yield *ca.* 0–4% *cis;* metals such as zinc, cadmium, tin, etc., in a variety of solvents, yield variable quantities of *cis* (<25%). We have tentatively suggested a carbonium ion process (eq 4) for the two-electron reductants, a radical process for the one-electron reductants, and a surface radical process for the metals. Three factors appear to determine the stereochemical course of these redox reactions, namely, the electronic (orbital) and conformational preference for *anti* over *syn* elimination and the nature of the reductant (mechanism).

Normally, 1,2 dehalogenation in solution occurs in the *anti* sense[2,3] as is shown in the following equation.

$$\underset{\textit{meso}\text{ or }\textit{dl}}{(C_6H_5CHBr)_2} + M \longrightarrow \underset{\textit{trans}\text{ or }\textit{cis}}{C_6H_5CH{=}CHC_6H_5} + MBr_2 \quad (1)$$

There are enough interesting cases of *syn* dehalogenation, however, to make decisions about the mechanism(s) equivocal.[3-7] In this survey of reductants, we posed two questions: could we find conditions under which the debrominations of the stilbene dibromides were clearly *anti*, and equally could we find conditions under which these debrominations were wholly *syn*?

As a reaction type, dehalogenation goes back a long time; iodide-promoted elimination was used on coumarin dibromide by Perkin[8] and has since been used in series as simple as the 1,2-diiodoethylenes[3] or as complex as steroid dibromides.[9] Variants on the dihalide may include substitution of hydroxy, alkoxy, acetoxy, tosylate, etc., for one or both of the halogen atoms.[2,10] Among the many possible dehalogenating agents are sodium in tetrahydrofuran[11] or liquid ammonia,[12] iron(II),[13] vanadium(II),[14] titanium(III),[14] cadmium,[15] lithium,[16] phosphines,[17] phosphites,[18] thiolates,[19] selenide,[20] acetate,[17] carbonate,[17] hydroxide,[19] triethyltin hydride,[21] cobalt(II),[22] etc.[9b] (see also below and Tables I and II). It is useful to look at the overall process (eq 1) either as a nucleophilic attack on positive halogen or as a redox process involving a two-electron reduction of the dihalide (oxidant).[10]

meso-Stilbene dibromide has frequently been chosen as a model compound. However, the results of debromination are always the same: under a wide variety of conditions, *trans*-stilbene is the exclusive product. Some results have been tabulated;[9b] we shall indicate several reductants here: ethanol,[23] phenyl-

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TABLE I

REDUCTIVE ELIMINATION REACTIONS OF *dl*-STILBENE DIBROMIDE[a]

Reductant	Conditions	*cis*-Stilbene, %[b]
NaI	Acetone	96
	DMF	90
	Acetonitrile	88
	1-Propanol	88
	MEK	95
	Ethanol[c]	93
	Glycol ether	92
	DMSO	89
	Methanol[d]	65
LiBr[e]	DMF 50–100°	16
K_2PtCl_4	DMSO	85
$C_6H_5SO_2Na$[f]	DMSO	88
	DMF	89
	Ethanol	...[g]
p-$CH_3C_6H_4SNa$[f]	Ethanol	>75[h]
	DMF	>75[h]
	DMSO	>75[h]
$LiAlH_4$[i]	THF, −10° (and 25°)	95 (and 50–65)
$NaBH(OCH_3)_2$[i]	Diglyme, 1 hr, 25°	0
$NaBH_4$[i]	Diglyme, 0.5 hr, 25°	25
NaH[j]	HMPA, 35°	27
$SnCl_2/HgCl_2$[e]	DMF, 25°	0
$SnCl_2$[k]	DMF, 50–75°	6 ± 3
$SnCl_2$	Ethanol	33–40[h]
	DMSO	26[h]
C_6H_5MgBr	Ether, 6 hr, *ca.* 25°	0
$Na_2S_2O_3$[l]	CH_3OH–$(CH_3)_2CO$ (3:1), 70–100°	Trace
β-Naphthol[l]	DMF, 25°	0
$(C_6H_5)_3P$	Toluene	0[g]
Di-*p*-tolylmercury[m]	$C_6H_5CH_3$, 25°, 4*d*	0
CuCl	Ethanol	...[g]
	DMF	0–5
	Ethanol, Dipy	0–5
	Ethanol, Py	0
	Ethanol, Pda	0
	Ethanol, Pyo	<15[h]
	Ethanol, Dma	...[h]
	DMSO	0–2
$FeCl_2$	Ethanol	...[g]
	Ethanol, Dipy	0–5
	Ethanol, PyO	2
	DMF	0
	DMSO	0
$CrCl_2$	Ethanol	0–4
	Ethanol, Dipy	0–1
	DMF	0–2
	DMSO	0–3
$TiCl_3$[n]	Ethanol	4
	DMF	12[h]
$CoCl_2$	Ethanol, NaCN	<32[h]

[a] The reactions were usually run for *ca.* 48 hr at the boiling point of the solvent or at 60–70° in the case of dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), unless otherwise specified. Other reagents are tetrahydrofuran (THF), methyl ethyl ketone (MEK), dipyridyl (Dipy), pyridine (Py), *o*-phenylenediamine (Pda), pyridine N-oxide (Pyo), and dimethylaniline (Dma). The reactions were complete, unless otherwise indicated. [b] This is the fraction of *cis*-stilbene in the *cis–trans* mixture. The actual yield may be lower. [c] Reference 34 reports 45 ± 10% reaction after 22 hr at reflux in 95% ethanol. The product contains 69 ± 5% *cis* isomer. [d] Reference 4 reports *ca.* 50% solvolysis products, *ca.* 30% *trans*-stilbene, and *ca.* 20% *cis*-stilbene. [e] Reference 6. The reaction mixture contains stannous chloride to reduce the bromine. In the absence of stannous chloride the product is 100% *trans*-stilbene. [f] R. Otto [*J. Prakt. Chem.*, **53**, 1 (1896)] and R. Otto and F. Stoffel [*Chem. Ber.*, **30**, 1799 (1897)] report 100% *cis* isomer with thiophenoxide in ethanol. [g] The reaction was incomplete after 48 hr at reflux temperature. [h] The per cent *cis* isomer is uncertain because of the presence of reagents which interfered with the analysis. [i] Reference 9. Lithium aluminum hydride promotes *cis–trans* isomerization. [j] P. Caubere and J. Moreau, *Tetrahedron*, **25**, 2469 (1969). Bibenzyl is also formed and sodium hydride promotes *cis–trans* isomerization. [k] Reference 7. [l] Reference 28. [m] Reference 32. [n] Titanium(III) reacts with DMSO.

hydrazine,[24] dimethylformamide,[5,7] potassium hydrosulfite,[25] sodium benzenesulfinate,[26] silver oxalate,[27] sodium thiosulfate,[28] lithium aluminum hydride,[9b,29] sodium methoxyborohydrides,[9a] copper(I),[30] pyridine,[31] di-*p*-tolymercury,[32] chromium(II),[33] tin(II),[7] magnesium,[12] copper,[34] zinc,[11,12,34] chloride,[6,35] bromide,[6,35] and iodide,[4,5,34,35] as well as the reductants in Tables I and II.

The debrominations of the *dl* dibromide display variable stereoselectivity (Tables I and II). This

TABLE II

METAL-PROMOTED ELIMINATION FROM *dl*-STILBENE DIBROMIDE[a–c]

Solvent[b]	*cis*-Stilbene in product, % Zn	Zn–Hg	Cd
Acetonitrile	3	...	26
Methanol	18	21	25
THF	11	...	28
$CH_3OCH_2CH_2OH$	11	...	24
Acetone	5	25	16
MEK	11	...	...
1-Propanol	15	...	21
Ethanol	14	14	12
Ethyl acetate	8	...	...
DMSO	25	...	25

[a] Reactions were normally carried out at the boiling point of the solvent for 4–5 hr. In DMF and DMSO the reaction temperature was 60–70°. [b] A few other reactions were carried out. The reductant, solvent, and per cent *cis*-stilbene were Cd–Hg, ethanol, 4%; Mg, DMSO, 45%; Al, DMSO, 53%; Pb, DMSO, 7%. Related work in the literature is as follows: Mg, THF, 10%;[12] Mg, THF, 65%; Cu, 95% C_2H_5OH, 18%;[34] and Zn, 95% C_2H_5OH, 13% [R. E. Buckles, J. M. Bader, and R. J. Thurmaier, *J. Org. Chem.*, 27, 4523 (1962)]; Zn, H_2O, 12%;[11,12] Zn, HCl (aqueous), 0% (Table I, footnote *f*). [c] Debrominations with several reductants (Zn, Zn–Hg, Cd, Cd–Hg, Mg, Al, Cu, Pb, and Sn) in DMF gave stilbene(s) apparently contaminated with bromostilbene (eq 2).

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dibromide is obviously more sensitive to the reductant and is also the one on which far less work had been done. Accordingly, we were most interested in it and surveyed its reactions with 17 reductants in one or more of 11 solvents. It is interesting that the most extensive and recent studies on reductive elimination deal with the reductant, chromium(II),[10] or several hydrides,[9] and a variety of disubstituted organic oxidants. We have varied the reductant widely and used only the stilbene dibromides as oxidants.

Experimental Section

The stilbene dibromides were prepared by standard methods: the *meso* form, mp 237–238°, from xylene; the *dl* form, mp 112–113°, from ethanol.[4,5] All of the other substances were reagent grade where possible. The zinc or cadmium amalgams were prepared from a mixture of the metal and mercuric chloride in aqueous hydrochloric acid. The amalgam was washed with water, filtered, and stored. Copper(I) chloride was a freshly prepared sample.

The composition of *cis–trans*-stilbene mixtures was determined by the absorbance ratio method on a Cary Model 14 spectrophotometer at 280, 290, 300, and 310 mμ.[4,36] Normally, the product mixture was treated with water and ether; after the ether extract was dried with calcium chloride, the solvent was evaporated and the residue was taken up in absolute ethanol to be analyzed. Under conditions of the debromination reaction, there was little or no isomerization of the *cis*-stilbene (Table III). The accuracy and precision of the stilbene analyses are suggested by the values in Table III—*i.e.*, *ca.* ±4%, absolute. Products of competing reactions can complicate matters, as we shall see.

TABLE III

ATTEMPTED ISOMERIZATION OF *cis*-STILBENE[a]

Reagent	Solvent	*cis*-Stilbene, %[b]
Zn, $ZnBr_2$	THF	97
	Ethanol[c,d]	96
	Acetone	98
	DMF	97
Cd, $CdBr_2$	DMF	98
	Acetone	97
	Ethanol	99
Fe^{2+}, Fe^{3+}	DMF	100
	Ethanol	100
	DMSO	96
Cr^{2+}, Cr^{3+}	DMF	99
	DMSO	100
Cu^{+}, Cu^{2+}	DMF	99
	DMSO	98
	Ethanol[d]	97
Sn^{2+}, Sn^{4+}	DMF	98
	DMSO	99
I^{-}, I_2	Acetone	100
	DMF	98
	DMSO	96
	Methanol	85[e]

[a] For reaction conditions see Table I, footnote *a*. [b] The uncertainty in the figure is probably <4%. [c] Reference 11 reports essentially no (<2%) isomerization under similar conditions. [d] Reference 34 reports essentially no isomerization under similar conditions. [e] At 100° in a sealed tube for *ca.* 11 hr.

Typically, the reactions were carried out with the stilbene dibromide (*ca.* 0.05 g) and an excess of reductant (*ca.* 1–2 g) in *ca.* 30 ml of solvent. Except for the solvents DMF and DMSO, reactions with the metals were carried out at reflux for *ca.* 4–8 hr. This "standard" period was insufficient for the metals copper, cadmium, lead, iron, and chromium in ethanol and acetone. Because DMF reacts with the stilbene dibromides at its boiling point,[6] reactions in it were carried out at 60–70°; these conditions were also used for DMSO. In these solvents, the reaction period was extended to 2 days for zinc, cadmium, zinc–cadmium amalgam, aluminum, and magnesium. Where the reaction was incomplete, the data are not usually given in Tables I and II. Besides isomerization of the product stilbenes, a possible complication in these reactions was dehydrobromination as in eq 2. The presence of either bromostilbene or tolan would,

$$(C_6H_5CHBr)_2 \xrightarrow{\text{base}} C_6H_5CH{=}CBrC_6H_5 \xrightarrow{\text{base}} C_6H_5C{\equiv}CC_6H_5 \quad (2)$$

of course, interfere with our analyses. *dl* dibromide with copper and cyanide ion in ethanol led to tolane. The diversion from eq 1 to eq 2 is also noted in Table II with some reagents.

Results and Discussion

In any attempt to account for stereoselectivity, we must remember that *trans*-stilbene is more stable than *cis*-stilbene in the range 25–150°: the *trans* to *cis* ratio is 500 at 25°.[37] By actual test, isomerization of the product stilbenes was usually small or negligible under typical reaction conditions (Table III). Although this establishes that we obtained products under kinetic control, there is no assurance that possible intermediates along the reaction path also retained their configurations.

Treated with diverse reductants, metals, anions, and cations, in several solvents, *meso*-stilbene dibromide gave *trans*-stilbene exclusively. For the most part, these reductants are the same as those given for the *dl* dibromide in Tables I and II and will not be listed separately. Clearly, our survey has not uncovered any reductant which could convert the *meso* dibromide by an overall *syn* process into *cis*-stilbene.

Since *all* reductants debrominate the *meso* dibromide stereospecifically in the *anti* sense to give the more stable *trans*-stilbene, little can be said about the elimination mechanism. For the two-electron reductants, orbital symmetry and orbital overlap as well as conformational factors favor the conventional E2 process.[2-7] For any reductants which may initiate a multistep process, the intermediates formed, *e.g.*, ionic, radical, or organometallic, are likely to be "set up" for subsequent conversion into *trans*-stilbene (eq 3 and 4).

Treated with diverse reductants, *dl*-stilbene dibromide gave a wide range of product compositions containing 0–96% *cis*-stilbene (Tables I and II). Judging from the products obtained it would appear that the mechanisms of elimination by two-electron, one-electron, and metallic reductants are different. For the nonmetal reductants, one can perhaps make the rough generalization that one-electron reductants give mainly *syn* elimination, and two-electron reductants give chiefly *anti* elimination. Unlike the results reported for the reaction of *dl*-2,3-dibromobutane and chromium(II),[10] the product ratio was not sensitive to changing solvent. Nevertheless, despite the fact that the role of the solvent is obscure[10] and sometimes unimportant (Table II), it does appear that the course of reductive elimination of the *dl* dibromide can be preselected.

With the two-electron reductants, *e.g.* Pt(II), RS^{-}, I^{-}, or H^{-}, one might suppose that the *dl* dibromide follows the concerted *anti*-elimination path to the

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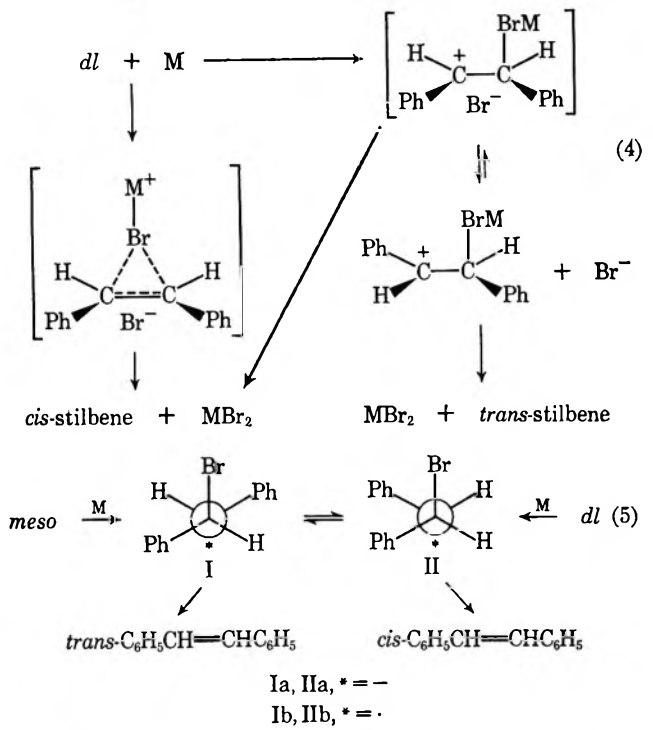
major product, *cis*-stilbene. The conformation of such a transition state necessarily involves *syn* phenyl–phenyl interactions. To alleviate this steric problem,

$$dl\text{-}(C_6H_5CHBr)_2 \xrightarrow{M} erythro\text{-}C_6H_5MCHCHBrC_6H_5 \xrightarrow{M} trans\text{-}C_6H_5CH{=}CHC_6H_5 \quad (3)$$

the *dl* dibromide may take a second path, one that is necessarily minor, since *trans*-stilbene is the minor product. Such a route could conceivably involve a concerted *syn* transition state, an SN2–E2 sequence (eq 3), a carbonium ion (eq 4), or a carbanion (eq 5) mechanism.[2,9b]



Ia, IIa, * = –
Ib, IIb, * = ·

Although there is no need to insist that any one path would hold for all of the reductants, the fact that the *dl* product ratio is not changed much by changes in two-electron reductant, solvent, or reaction temperature suggests that we are dealing with one mechanism. Furthermore, this apparent similarity in the product-determining steps indicates to us that we are dealing with the partitioning of one or more reactive intermediates. Put another way, two fast processes with low activation enthalpies (or free energies) are likely to have smaller differences ($\Delta H_t^{\ddagger} - \Delta H_c^{\ddagger}$) than two slow processes with high activation enthalpies. Finally, the intermediate or intermediates must be sufficiently short lived so as to preclude equilibrations, for this can only lead to the more stable *trans*-stilbene.

For these reasons, we believe that the *dl* dibromide is debrominated on one of those paths (eq 4) analogous to those proposed for bromine additions to alkenes.[38,39]

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It is known that bromine additions to *cis*-stilbene can be *anti* stereoselective; in nonpolar solvents (dielectric constant, ϵ 2–3) the amount of *dl* dibromide is *ca.* 90–100%. As ϵ increases to *ca.* 35, the amount of *meso* dibromide has become *ca.* 80–100%; the presence of bromide ion in the polar solvents decidedly increases the relative yield of *dl* dibromide.[34,40] In eq 4, the formation of a configurationally oriented positive ion, whether cyclic or acyclic, assists in the slow step. Subsequently, the formation of some unencumbered carbonium ion allows leakage into the sequence from *meso*- to *trans*-stilbene.

A two-electron carbanion process[11] (eq 5) cannot be completely discounted at this stage, although we consider it less probable. The carbanions could form from any one of the three *dl* rotomers, and there appears to be no obvious reason why the rotomer IIa pictured should be favored, either in its formation or, subsequently, by internal rotation of the other two rotomers. It would seem, in fact, that this mechanism provides for *too easy* leakage of the *dl* carbanions to Ia by inversion and rotation of the carbanion, processes which would lead to *trans*-stilbene as the major product.

We come now to the one-electron reductants of the *dl* dibromide, which appear at the bottom of Table I. These range from ferrous and chromous species to others such as hydride, tin(II), and thiosulfate, whose purported one-electron character in a given reaction would have to be established. Based on their product pattern, however, we propose the gross radical mechanism of eq 5 for all of these reductants. The radical first formed is a relatively stable benzylic species. Before it encounters another molecule of reductant, it presumably equilibrates with Ib by internal rotation. We further assume that specific reductants can at best modify the product-forming steps only in a minor way.

The reductions of *dl* dibromides by metals gave results (Table III) difficult to interpret. Curiously, all of these debrominations yielded some *cis*-stilbene; some of the yields were solvent sensitive. There have been indications in the past that certain metal debrominations may display a variable stereoselectivity.[11,12,34,41] Our results show that this is general. Concerning the mechanism(s), we believe that "free" ions or radicals can probably be excluded as intermediates, since they would have been susceptible to capture by protonation or solvolysis in at least some of our solvents. Here, it appears that a given reductant had a specific role right up to the product-determining steps. Whether this involved ion or radical pairs and possibly the metal surface is not clear in detail, but some variant of this seems necessary to account for the data.

Registry No.—*dl*-Stilbene dibromide, 13627-48-0.

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Nuclear Magnetic Resonance Study of Alkyl Chloride Behavior in Aluminum Bromide–Chlorobenzene

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An nmr study of alkyl chlorides in the $AlBr_3$–chlorobenzene system at −50° provides evidence for the detection of a mobile *t*-amyl cation. The ion is involved in equilibria with the solvent leading to rapid scrambling of aromatic protons, and it may be cleanly trapped by hydride donors. Secondary cations are not detected in this system, but their presence as intermediates may be indirectly inferred from their reactions with hydride donors.

Aluminum bromide is a strong Lewis acid which has been extensively studied as a catalyst for paraffin isomerization and similar processes. These are thought to involve the formation of alkyl cationic intermediates which often rearrange and participate in facile hydride transfer reactions. Several years ago it was suggested that stable alkyl cations could be detected by nmr studies of alkyl halides in solutions containing antimony pentafluoride.[1] Tertiary cations are particularly easy to form and their spectra are characterized by substantial downfield shifts of groups α to the charged carbon.

In view of the large body of information about cations which have developed from these techniques it is somewhat surprising that nmr has been scarcely applied to the study of the aluminum bromide system. In 1967 it was reported that solutions of aluminum bromide in 1,2,4-trichlorobenzene could initiate and support extremely long chain hydride transfer processes between isobutane and low concentrations of *t*-butyl cations.[2] The rapid intermolecular hydride transfer reaction collapses the methyl doublet in isobutane's nmr spectrum, but since the ion concentration is low there is no detectable shift in its position. The nmr spectrum of 1,2,4-trichlorobenzene is nearly unchanged while the hydride exchange is occurring so that, if any proton exchange with solvent is going on simultaneously, it must be relatively slow. To a first approximation it thus appears that cation interaction with the solvent is small and one might hope to ionize a sufficient amount of *t*-butyl chloride in $AlBr_3$–1,2,4 trichlorobenzene to be detected by nmr. However, it has been our experience that *t*-butyl chloride does not simply ionize but at ambient conditions eliminates HCl and forms isobutylene which reacts *via* a myriad of paths as in sulfuric acid,[3] to produce a complex nmr spectrum, presumably of allyl ions. One doesn't know whether the elimination of HCl reflects an inherently lower acidity of the HCl–$AlBr_3$ system compared with HF–SbF_5 or if 1,2,4-trichlorobenzene is simply too basic a solvent with which to confine the latently reactive *t*-butyl cation. Unfortunately, trichlorobenzene freezes at 17° and, although supercooled solutions can be prepared, it is inconvenient for studies at low temperatures.

A number of potentially useful solvents have been investigated for their compatibility with *t*-alkyl ions and aluminum bromide at low temperatures. This report deals with the chlorobenzene–aluminum bromide system, a more basic medium then 1,2,4-trichlorobenzene which however can be used at −50° and which supports a limited range of cationic reactivity. The nmr spectra to be discussed are not so easily related to the presence of "stable" cations as are those obtained with SbF_5, but their detection seems plausible when the spectra are considered with the results of hydride transfer trapping experiments.

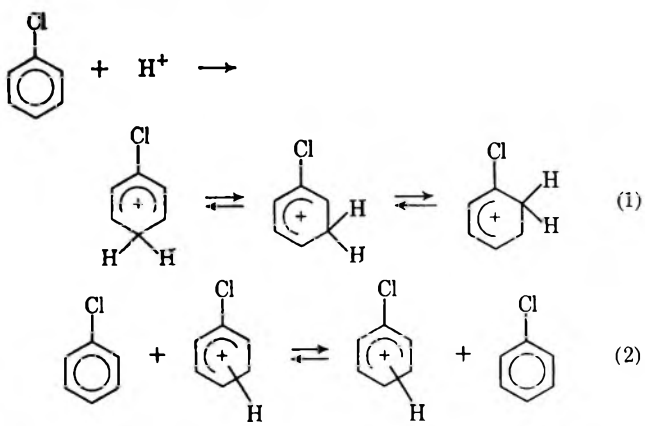
Experimental Section

Half molar solutions of redistilled aluminum bromide in chlorobenzene dried with barium oxide or 13-X molecular sieves were used throughout. At −50° the nmr spectra of these solutions were the same as that of neat chlorobenzene. At room temperature, however, the solvent's spectrum was partially collapsed, probably owing to trace amounts of moisture in the aluminum bromide. The background exchange could be stopped by adding small amounts of more basic hydrocarbons such as mesitylene to the system but neither repeated distillation of $AlBr_3$ nor the use of sublimed $AlBr_3$ eliminated this reactivity.

Alkyl halides were added to these solutions at or below the temperature of the nmr scan. Carbonium ion intermediates were conveniently trapped by adding hydride donors, paraffins, or naphthenes to the nmr tubes and shaking vigorously for a few seconds at reaction temperature. The nmr spectra of the resulting solutions, could be examined and the products recovered by vacuum distillation for gas chromatographic analysis.

Results and Discussion

The 60-Mc nmr spectrum of chlorobenzene is complex and exhibits considerable fine structure.[4] The spectrum while unaffected by the presence of $AlBr_3$ at −50° may be collapsed by the subsequent addition of catalytic quantities of HCl or HBr, Figure 1. The change in the spectrum is indicative of the existence of an exchange process resulting in the rapid equilibration of all solvent protons. Such a process probably involves both intra- and intermolecular proton migration, eq 1 and 2. At high rates of exchange the spectrum is a



(1) (a) G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffatt, I. J. Bastien, and E. B. Baker, *J. Amer. Chem. Soc.*, **85**, 1328 (1963); (b) G. A. Olah, E. B. Baker, J. C. Evans, W. S. Tolgyesi, J. S. McIntyre, and I. J. Bastien, *ibid.*, **86**, 1360 (1964).

(2) G. M. Kramer, B. E. Hudson, and M. T. Melchior, *J. Phys. Chem.*, **71**, 1525 (1967).

(3) N. Deno, H. G. Richey, Jr., J. D. Hodge, J. J. Houser, and C. U. Pittman, Jr., *J. Amer. Chem. Soc.*, **85**, 2991 (1963).

(4) S. Castellano, R. Kostelnik, and C. Sun, *Tetrahedron Lett.*, 4635 (1967).

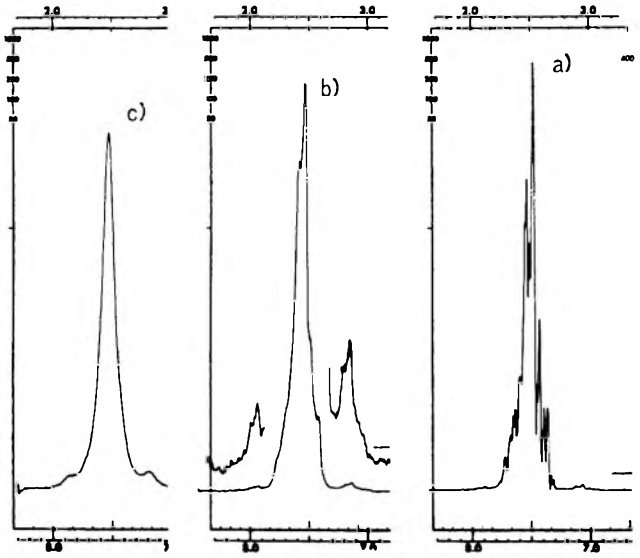
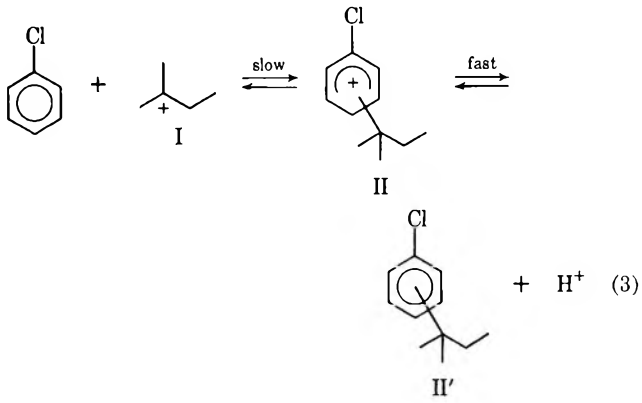


Figure 1.—The spectrum of chlorobenzene-containing 0.5 *M* $AlBr_3$ at −50°: (a) neat; (b) +0.02 *M* HCl; (c) +0.2 *M* HCl.



enough on nmr time scale to permit the apparent observation of ions I and II, the latter in rapid equilibrium with an undetermined amount of amyl chlorobenzenes.

The spectrum of 0.2 *M* *t*-amyl chloride in the 0.5 *M* $AlBr_3$–chlorobenzene solution at −50° is characterized by a multicomponent peak centered at −0.88 ppm, a singlet at −2.63 ppm, and a broad peak at −3.57 ppm

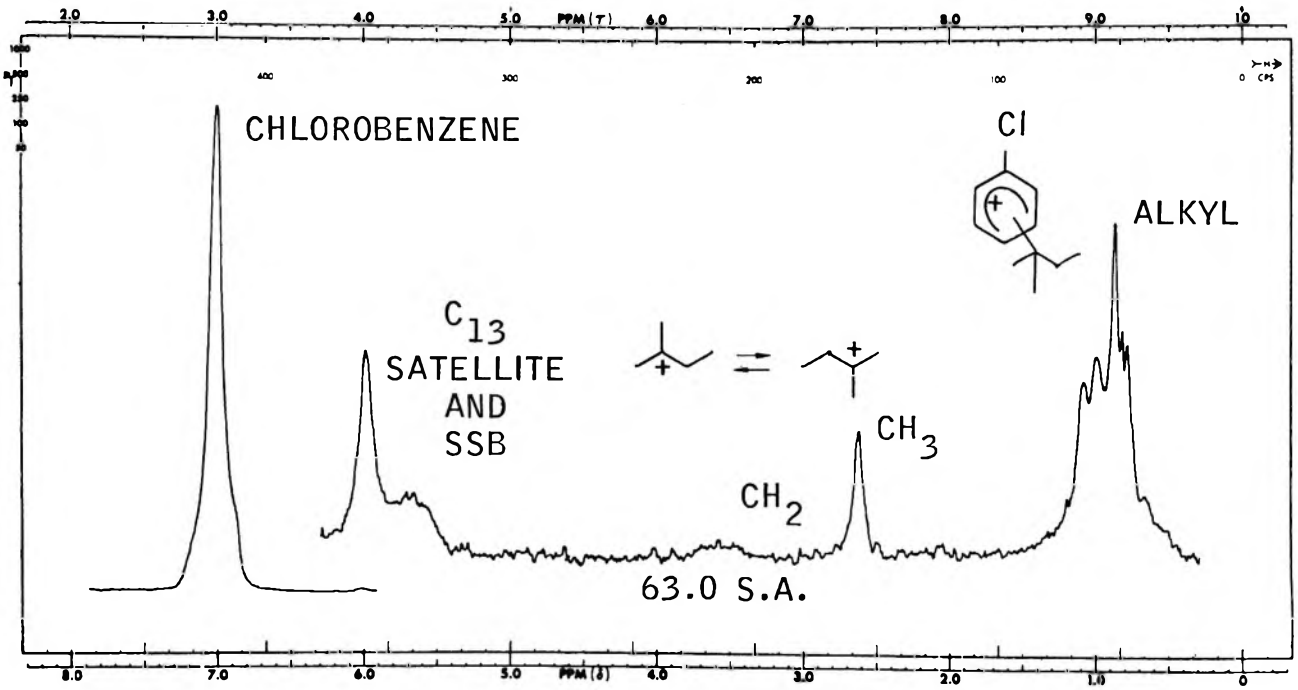
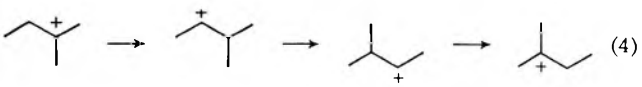


Figure 2.—The spectrum of 0.16 *M* *t*-$C_6H_{11}Cl$ in chlorobenzene-containing 0.5 *M* $AlBr_3$, at −50°.

singlet centered at −7.00 ± 0.02 ppm (referred to TMS as an internal reference). The lifetime of solvent molecules under these conditions ought to be between 0.01 and 0.1 sec. Unfortunately, we do not have the means of quantitatively evaluating the exchange rates and energetic parameters from the spectral data.

A similar collapse of the solvent spectrum is caused by the addition of *t*-butyl, *t*-amyl, or isopropyl chloride or bromide. This indicates that the halides form cations which either add to or protonate chlorobenzene thus initiating the exchange. At this time the spectrum of the alkyl halide is immediately altered. The tertiary halides yield a number of bands which are most easily interpreted in terms of an equilibrium between tertiary cations + solvent and the alkylated solvent, eq 3. The equilibrium is attained rapidly, but slowly (Figure 2). The singlet at −2.63 ppm and the broad band at −3.57 ppm are assigned to the *t*-amyl cation undergoing rapid equilibration of the methyl groups, possibly by intramolecular hydride and methide shifts (eq 4). These shifts lead to the time-averaged


(4)

equilibration of all methyl groups in the ion and are responsible for the −2.67-ppm singlet. Such an explanation has been proposed by Olah to account for the coalescence of the separate methyl resonances of the stable cation upon heating to +90° in HSO_3F–SbF_5,[5]

(5) G. A. Olah and J. Lukas, *J. Amer. Chem. Soc.*, **89**, 2227 (1967).

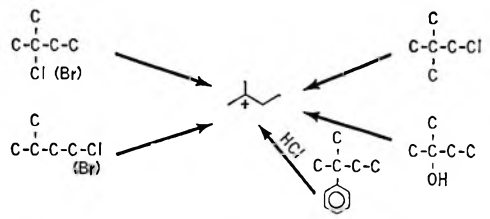


Figure 3.—Precursors forming the *t*-amyl cation.

the results of trapping with many hydride donors and the ease with which it is obtained from many precursors.

The −2.63-ppm peak contains about 10% of the combined area of the −0.88, −2.63, and −3.57 peaks. The peak area is proportional to the *t*-amyl chloride concentration up to an RCl:$AlBr_3$ ratio of 0.4:1 but falls off at much higher values, possibly because of a

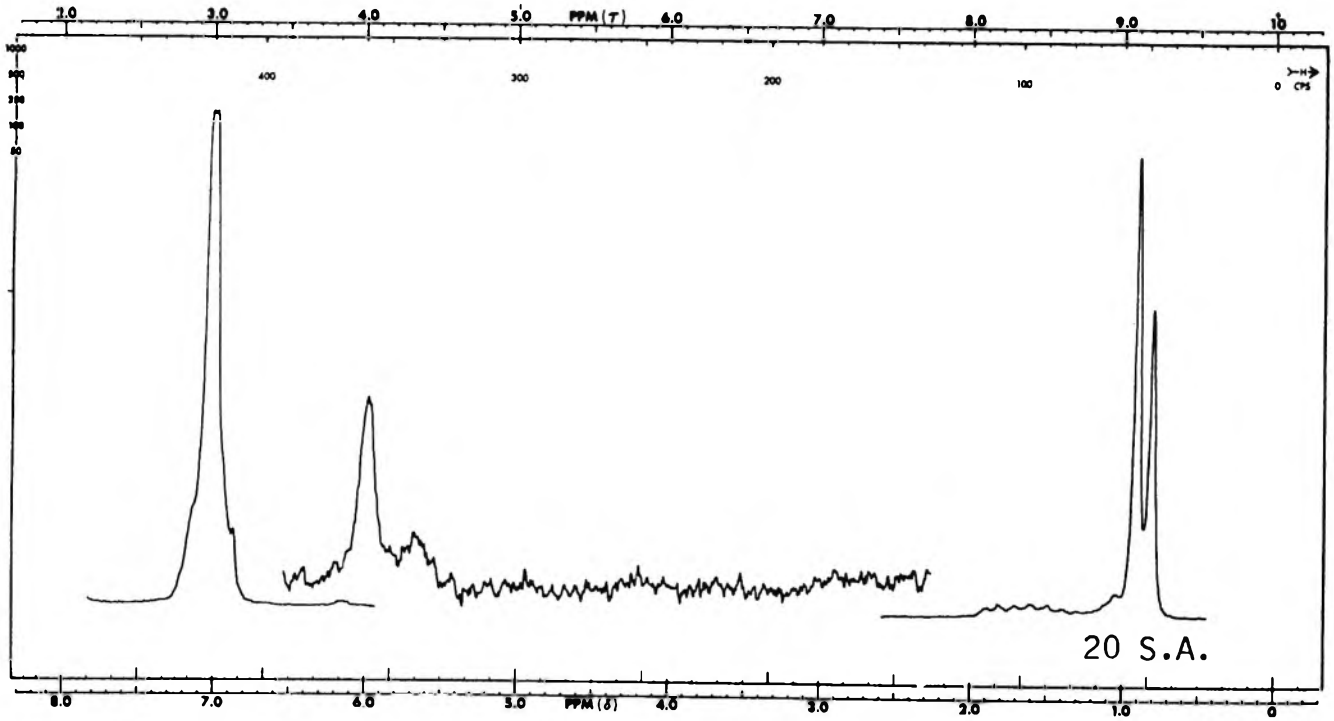


Figure 4.—The spectrum of isobutane after reacting with 0.16 *M* *t*-$C_5H_{11}Cl_3$, −50° (*i*-C_4H_{10}:*t*-$C_5H_{11}Cl$ = 25:1). Isobutane's spectrum is broadened owing to intermolecular hydride transfer, *i*-C_4H_{10} + *t*-$C_4H_9^+ \rightleftharpoons$ *t*-$C_4H_9^+$ + *i*-C_4H_{10}.

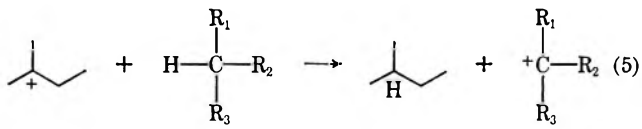
or at much lower temperatures in SbF_5–SO_2FCl solution.[1b] With SbF_5, the position of the collapsed methyl peak is at −3.60 ppm, 1 ppm further downfield than in chlorobenzene. The peak position probably is due to several factors, namely that the ion may exist in equilibrium with small concentrations of alkyl chlorides, bromides, or amylenes and it may also be subject to specific solvation by chlorobenzene, a factor often leading to upfield chemical shifts.[6] In any case the spectrum indicates that the *t*-amyl cation is a major component of these equilibria.

The band at −3.57 ppm is assigned to the methylene protons. Saunders has shown that the CH_2 band in the SbF_5–SO_2FCl system contains extensive fine structure,[7] which is lost in SbF_5–HSO_3F and hardly apparent in $AlBr_3$–chlorobenzene. The fine structure has been taken as evidence that rearrangements of the *t*-amyl cation in SbF_5–SO_2FCl involve strictly intramolecular processes. If intermolecular proton exchange were to occur rapidly, coupling to the CH_2 group would be reduced and ultimately eliminated. The broad CH_2 band in $AlBr_3$–chlorobenzene thus suggests that proton exchange occurs at modest rates in this system.

Evidence that the spectrum is probably that of the *t*-amyl ion comes not only from the nmr but also from change in stability of the ionic complexes from those initially involving dimeric aluminum bromide to those with the monomer.

Spectra equivalent to that obtained with *t*-amyl chloride have been obtained with 1-chloro-3-methylbutane, 1-chloro-2,2-dimethylpropane, *t*-amyl alcohol, *t*-amylbenzene + HCl, and similar compounds (Figure 3). 1-Chloropentane and 2-chloropentane do not appear to isomerize to the tertiary ion. In this respect the system differs from neat SbF_5 which permits a ready isomerization of the secondary cations.

The −2.63-ppm peak is immediately removed from the spectrum by shaking the nmr tube with an excess of a tertiary hydride donor at −50°, eq 5. The resulting



(5)

spectrum is then essentially that of the donor rapidly transferring hydride ions to a small concentration of skeletally similar ions. When the donor is isobutane this process may broaden and coalesce its doublet to a singlet.[2] Vacuum distillation from the sample tube leads to a clean recovery of isopentane. While yields are somewhat biased in favor of the light component by this procedure the recovery of isopentane is approxi-

(6) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Inc., New York, N. Y., 1959, p 427.

(7) M. Saunders and E. L. Hagen, *J. Amer. Chem. Soc.*, **90**, 2436 (1968).

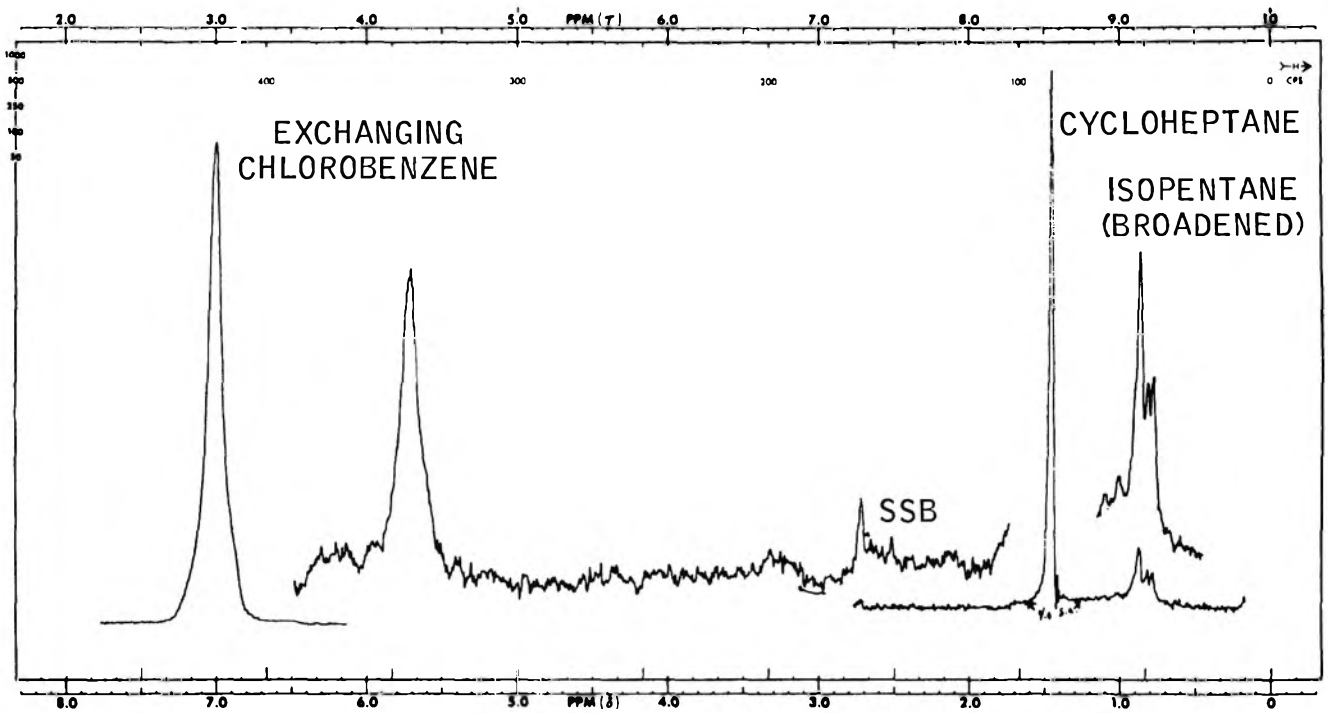


Figure 5.—Isopentane is trapped by reaction of 0.16 *M* *t*-$C_5H_{11}Cl$ in 0.5 *M* $AlBr_3$–chlorobenzene with cycloheptane at 50° (cycloheptane: *t*-amyl chloride = 25:1).

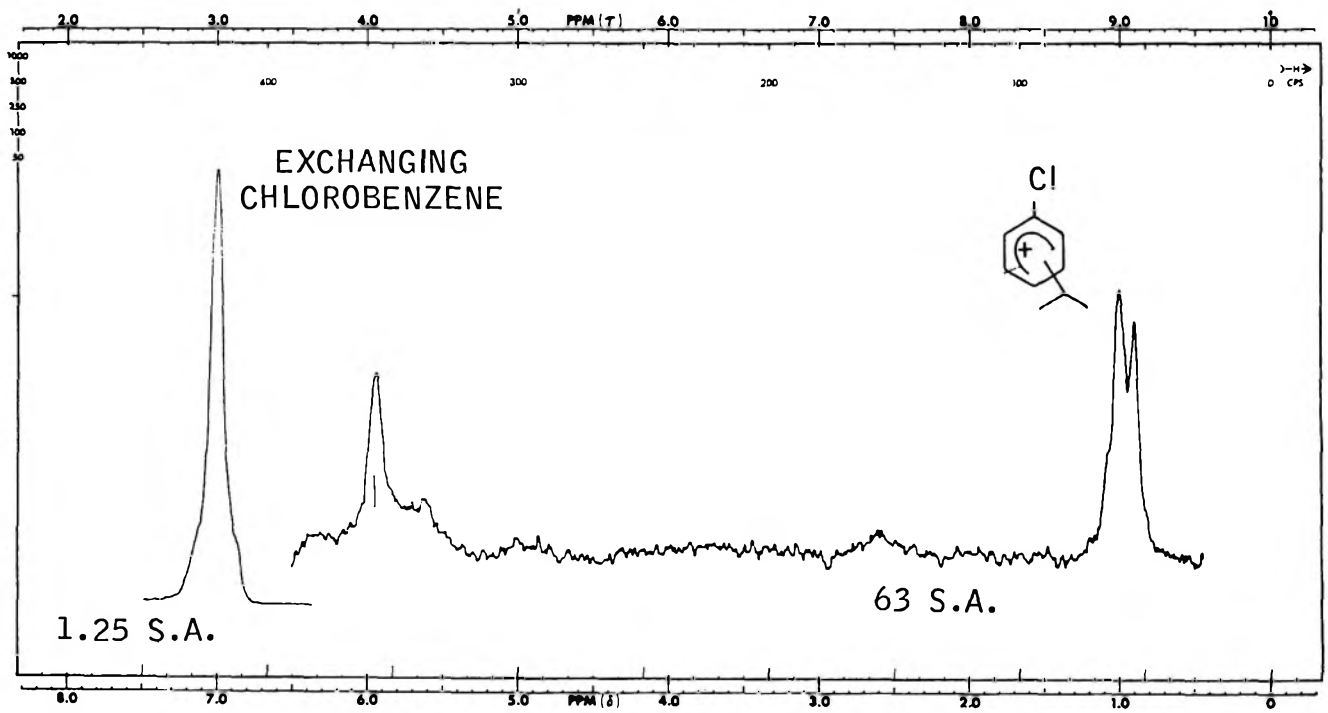


Figure 6.—The spectrum of 0.16 *M* *i*-C_3H_7Cl in 0.5 *M* $AlBr_3$–chlorobenzene, −50°.

mately quantitive. Similar experiments have been carried out with 2,3-dimethylbutane, 2,2,3-trimethylbutane, and methylcyclopentane as donors. The nmr spectrum of a typical reaction with isobutane is shown in Figure 4.

The −2.63-ppm peak is also destroyed upon reaction with secondary hydride donors such as *n*-hexane, cycloheptane, and cyclooctane at −50°. Isopentane is again recovered but the nmr spectra of these compounds does not undergo much change. This would be consistent with hydride transfer from secondary sources being slow on the nmr time scale but fast enough to reduce the half-life of the *t*-amyl cation to less than several minutes. Rearrangement of the secondary donors is slow at −50° but isomerization of the naphthenes can be detected.

The isopentane formed by reaction with cycloheptane appears to participate in rapid hydride transfer with a small concentration of residual *t*-amyl cations, thus broadening its spectrum (Figure 5). Cycloheptane's nmr spectrum remains a single sharp line while this occurs. A corresponding experiment with cyclooctane leads to isomerization of the naphthene and interference with isopentane's spectrum.

The nmr spectrum of *t*-butyl chloride is a singlet at −1.4 ppm. In the $AlBr_3$–chlorobenzene system at −50°, 0.2 *M* solutions of *t*-butyl chloride exhibit a very small peak at −4.1 ppm which may be the cation and a closely spaced pair of peaks at −0.98 ppm with a spacing of 2–3 cps. The small peak diminishes as the temperature is raised, is not visible at −10°, but reappears upon cooling to −30. The upfield peaks also undergo a reversible change in relative intensity with temperature. *t*-Butyl bromide under similar conditions yields only one upfield peak.

The small and rather broad peak at −4.1 ppm suggests that the *t*-butyl cation is undergoing proton exchange with HX or the solvent. There is no simple explanation for the different spectral behavior of *t*-butyl chloride and bromide but the spectra may be readily obtained from isobutyl halides or *t*-butyl benzene + HX and isobutane is cleanly recovered from any of the systems by reaction with hydride donors. The spectra are not obtained with the normal butyl halides.

While the nmr study of tertiary cation sources in $AlBr_3$–chlorobenzene provides some evidence for the presence of relatively stable ions, no indication of stable secondary ions has been found by similar means. Isopropyl chloride's spectrum is, however, immediately altered in this system (Figure 6). The methyl doublet shifts upfield and broadens noticeably and the methine proton's septet also moves upfield and broadens. The same spectrum is obtained with 1-chloropropane and there is no evidence of low field peaks attributed to the isopropyl cation.[1b]

On the other hand, chlorobenzene's spectrum collapses to a singlet indicating the formation of an alkyl aromatic cation like III. Attempts to trap propyl cations by hydride transfer from methylcyclopentane lead to the formation of only small amounts of propane, 1 to 5% of theory. Again, small yields of propane are obtained if the alkyl cations are generated by the addition of HCl to isopropylbenzene. Isopropylbenzene rapidly reacts, however by, transferring the alkyl group to chlorobenzene generating the 3 isopropyl chlorobenzenes.[8]

The behavior of isopropyl chloride and cumene leads to the conclusion that the nmr spectrum is probably that of a system conatining mainly protonated isopropyl chlorobenzenes. The isopropyl groups are considered to be involved in rapid disproportionation reactions between solvent molecules. Broadening of the alkyl protons is attributed both to the alkyl exchange which interconverts *ortho*, *meta*, and *para* isomers and to reversible protonation of the alkylchlorobenzenes which rapidly alters the environment of the alkyl group.

We do not understand why the addition of methylcyclopentane to protonated isopropyl chlorobenzene should only yield small quantities of propane. If the ion III were in rapid equilibrium with chlorobenzene and an isopropyl cation, quantitative recovery of propane might be anticipated. A possible explanation has been tendered by our colleagues, namely that III is in resonance with IIIa and may contain a proton of sufficient acidity to abstract hydride from methylcyclopentane. If this reaction was fast while ionization was slow it could account for our results, but this possibility has not been investigated.

(8) Determined by gas chromatography and mass spectroscopy after quenching the system in water.

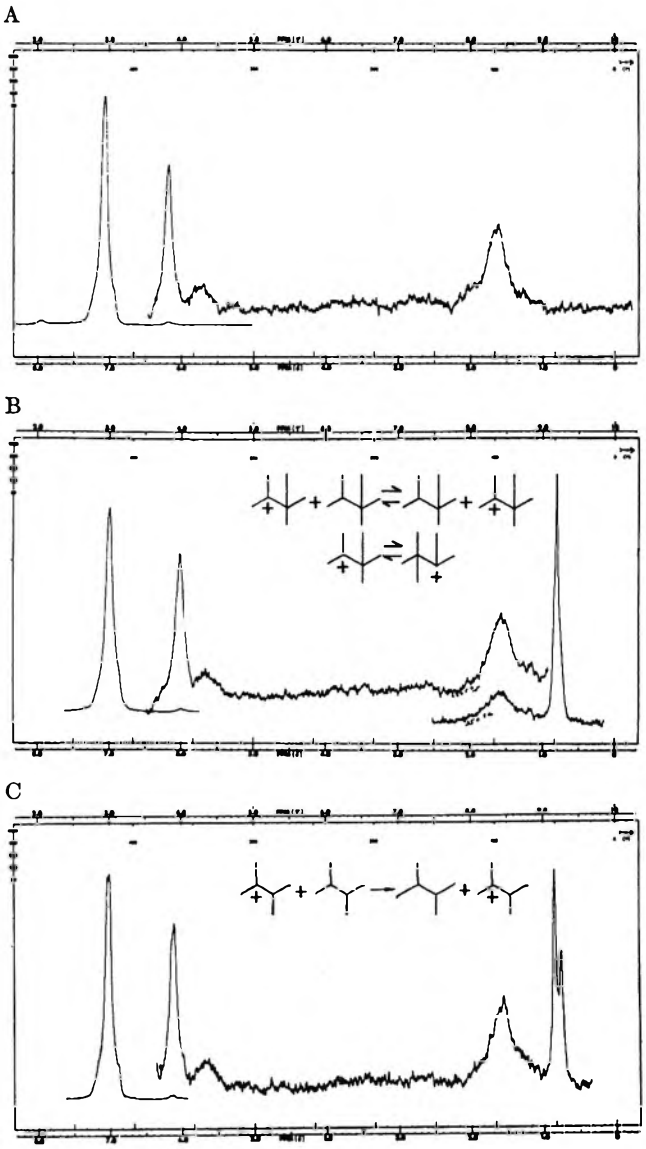
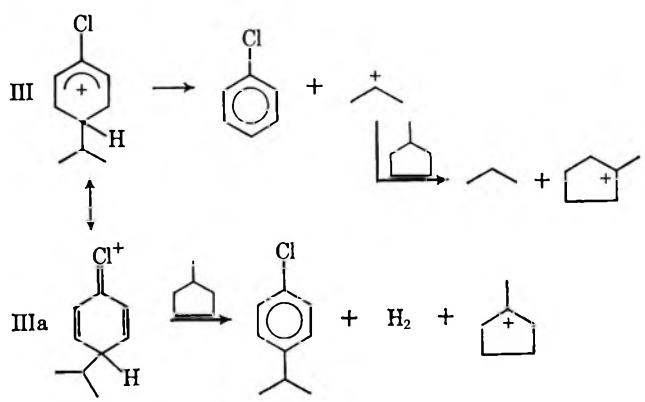


Figure 7.—The spectrum of 0.16 *M* bromocyclopentane in 0.5 *M* $AlBr_3$–chlorobenzene at −50°: (A) alone; (B) 0.1 *M* 2,2,3-trimethylbutane added; (C) 0.1 *M* 2,3-dimethylbutane added.



Although isopropyl chloride does not form a stable secondary ion the formation of some propane indicates their presence as reactive intermediates. Other secondary sources such as cyclopentyl and cyclohexyl

halides also react with tertiary hydride donors. The nmr spectrum of the cyclic halide is but slightly affected as the reaction appears to generate tertiary ions which initiate hydride transfer chain reactions with the remaining donor molecules. For example, reaction with 2,2,3-trimethylbutane and 2,3-dimethylbutane leads to immediate exchange broadening of the paraffins spectra (Figure 7). The spectra indicate that methyl migration is rapid in the former system. These halides also initiate the rearrangements of cycloheptane or cyclooctane which however occur slowly at −50°.

Thus in the $AlBr_3$–chlorobenzene system hydride transfer from tertiary or secondary sources to tertiary or secondary cations has been observed at quite low temperatures. Spectra of solutions of tertiary halides contain bands consistent with the presence of tertiary cations. The bands may be removed by reaction with hydride donors and hydrocarbons of the proper structures cleanly recovered. High field nmr bands are also present which suggest the presence of protonated alkyl aromatics.

Registry No.—Chlorobenzene, 108-90-7; *t*-amyl chloride, 594-36-5; isobutane, 75-28-5; cycloheptane, 291-64-5; *t*-butyl chloride, 507-20-0; isopropyl chloride, 75-29-6; bromocyclopentane, 137-43-9.

The Formation of Sulfur–Sulfur Bonds by the Chloramination of Thiols[1]

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Chloramine and dimethylchloramine react with cyclohexylmercaptan, thiophenol, 2-mercaptonaphthalene, 2-mercaptopyridine, 2-mercaptoethanol, 1-butanethiol, and 1,2-ethanedithiol with the extraction of the thiol hydrogen atoms and the formation of sulfur–sulfur bonds. There is an indication that the first step in the reaction is the formation of compounds of the type $RSNH_2$ or $RSN(CH_3)_2$. Possible mechanisms for the chloramination reactions are discussed.

It has been well established that the chloramine molecule reacts with electron-donor molecules in accordance with the equation

$$B: + NH_2Cl \longrightarrow [B:NH_2^+]Cl^-$$

where B: is the Lewis base. Among the Lewis bases studied are those containing nitrogen, phosphorus, arsenic, or antimony atoms as the basic centers of the molecule. During the past decade, the reactions of chloramines of the type $R_2'NCl$, where R′ = H or alkyl, with amines, phosphines, arsines, and stibines have been extensively investigated in this laboratory.[2-13]

We were interested in studying the reactions of chloramines with compounds in which sulfur is the electron-donor atom. We hoped that such reactions of $R_2'NCl$ (R′ = H or alkyl) with thiols would result in the cleavage of the N–Cl bonds in the chloramine molecules with the formation of sulfenamides of the types $RSNH_2$ and $RSN(CH_3)_2$. Previous work reported in the literature indicating that aqueous solutions of chloramine react with alkali metal mercaptides to yield insoluble sulfenamides[14-18] supported this suggestion. In all these cases, ammonia was present in excess.

It was our thinking that formation of the disulfide is the initial step in these reactions and that the sulfenamide is obtained by the cleavage of RS–SR to $RSNH_2$ and RSCl followed by the formation of a second molecule of $RSNH_2$ by ammonolysis of RSCl. This thinking was based on the reported formation of disulfides by oxidation (by means other than chloramination) of thiols.[19]

Therefore, when we observed that cyclohexylmercaptan reacts with dimethylchloramine in ethereal solution to give dicyclohexyl disulfide in good yield, we decided to investigate the series of reactions to determine if the sulfenamides, as well as the disulfides, could be obtained and under what conditions. We were also interested in the possibility of forming $[RSN]_n$ polymers.

Carr and coworkers[15] had found the presence of some disulfides in their oxidation of mercaptides to sulfenamides in aqueous media and had speculated concerning the mechanism of the reactions.

The results of the research we report here show that the disulfide is obtained almost exclusively from the chloramination of thiols in ethereal solution with either chloramine or dimethylchloramine. The presence of ammonia in the reactions with chloramine does not change the result. The results indicate the probability

(1) (a) This research was reported at the 22nd meeting-in-miniature of the Florida Section of the American Chemical Society, Jacksonville, Fla., May 1969.

(2) (a) H. H. Sisler, A. Sarkis, H. S. Ahuja, R. J. Drago, and N. L. Smith, *J. Amer. Chem. Soc.*, **81**, 2982 (1959). (b) W. A. Hart and H. H. Sisler, *Inorg. Chem.*, **3**, 617 (1964).

(3) D. F. Clemens and H. H. Sisler, *ibid.*, **4**, 1222 (1965).

(4) H. H. Sisler and C. Straton, *ibid.*, **5**, 2003 (1966).

(5) S. R. Jain, L. K. Krannich, R. E. Highsmith, and H. H. Sisler, *ibid.*, **6**, 1058 (1967).

(6) R. L. McKenney and H. H. Sisler, *ibid.*, **6**, 1178 (1967).

(7) H. H. Sisler and S. R. Jain, *ibid.*, **7**, 104 (1968).

(8) R. E. Highsmith and H. H. Sisler, *ibid.*, **7**, 1740 (1968).

(9) K. Utvary and H. H. Sisler, *ibid.*, **7**, 698 (1968).

(10) K. Utvary, H. H. Sisler, and P. Kitzmantel, *Monatsh. Chem.*, **100**, 401 (1969).

(11) R. E. Highsmith and H. H. Sisler, *Inorg. Chem.*, **8**, 1029 (1969).

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(13) S. R. Jain and H. H. Sisler, *ibid.*, **8**, 1243 (1969).

(14) T. J. Hurley and M. A. Robinson, *J. Med. Chem.*, **8** (6), 888 (1965).

(15) E. L. Carr, G. E. P. Smith, and G. Alliger, *J. Org. Chem.*, **14**, 921 (1949).

(16) S. B. Greenbaum, *J. Amer. Chem. Soc.*, **76**, 6052 (1954).

(17) I. G. Farbenind, German Patent 586,351 (1933).

(18) J. A. Baltrop and K. J. Morgan, *J. Chem. Soc.*, 3072 (1957).

(19) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol I, Chemical Publishing Co., Inc., New York, N. Y., 1958, pp 120–126.

TABLE I

CHLORAMINATION REACTIONS WITH THIOPHENOL AND CYCLOHEXYLMERCAPTAN IN DIETHYL ETHER

Reactants[a] A	B[b]	Mole ratio (A:B)	Products[c]	Mp or bp, °C (mm)	Yield, %
$(CH_3)_2NCl$	C_6H_5SH	1:2	$C_6H_5S-SC_6H_5$[d]	57–58[e]	74.3[f]
				175–185[g] (14)	
C_6H_5SH[h]	$(CH_3)_2NCl$	1:1	$C_6H_5S-SC_6H_5$[i]	55–56	85.0[j]
NH_2Cl (+ NH_3)	C_6H_5SH	1:2	$C_6H_5S-SC_6H_5$	55–56	86.0[f]
C_6H_5SH[h]	NH_2Cl (+ NH_3)	1:2	$C_6H_5S-SC_6H_5$	54–55	93.1[j]
C_6H_5SH[h]	NH_2Cl (ammonia free)	1:1	$C_6H_5S-SC_6H_5$	52–53	80.8[j]
$(CH_3)_2NCl$	$C_6H_{11}SH$	1:2	$C_6H_{11}S-SC_6H_{11}$[k]	140 (2.1)	86.1[f]
$C_6H_{11}SH$[h]	$(CH_3)_2NCl$	1:1	$C_6H_{11}S-SC_6H_{11}$	150–152 (4)	77.5[j]
NH_2Cl (+ NH_3)	$C_6H_{11}SH$	1:2	$C_6H_{11}S-SC_6H_{11}$	190 (18)	56.8[l]
$C_6H_{11}SH$[h]	NH_2Cl(+ NH_3)	1:1	$C_6H_{11}S-SC_6H_{11}$	157 (4.3)	87.5[j]

[a] A added dropwise to B. [b] Taken in slight excess of specified mole ratio. [c] Dimethylammonium chloride and ammonium chloride formed from $(CH_3)_2NCl$ and NH_2Cl, respectively, were obtained in almost quantitative yields. [d] Yellow-white needles recrystallized from hot absolute alcohol. [e] Melts to give a yellow liquid; color deepens on heating. [f] Based on chloramine. [g] Solidifies in condenser; hot-water condenser was used. [h] In the initial stages, transient color changes of the reaction mixture were observed (from light yellow to orange red). [i] Repeated at a temperature of 0–5; same products were obtained. [j] Based on mercaptan. [k] Yellowish, oily liquid; purity was checked by vpc. [l] Based on mercaptan used; reaction probably was not completed.

that, contrary to our initial expectation, the formation of the sulfenamide is the initial step in the reaction and the disulfide results from reaction of the sulfenamide with additional thiol.

Experimental Section

Materials.—Cyclohexylmercaptan, 2-mercaptopyridine, thiophenol, 2-naphthalenethiol, and diphenyl disulfide were obtained from K & K Laboratories. 1-Butanethiol and dibutyl disulfide were obtained from Eastman Organic Chemicals. 2-Mercaptoethanol and 1,2-ethanedithiol were obtained from the J. T. Baker Chemical Co. The purity of the mercaptans and the disulfides was checked by comparison of indices of refraction, densities, melting or boiling points, and infrared spectra with the corresponding data in the literature. All solvents used were of reagent grade and were stored over calcium hydride. Absolute ethanol was used as received.

Analyses.—The Galbraith Microanalytical Laboratory conducted the elemental analyses. In some cases, the ordinary Kjeldahl procedure for nitrogen analysis was employed in this laboratory. Chlorine analysis was also done in this laboratory. Molecular weights were determined by the cryoscopic method. Melting points were obtained with a Thomas–Hoover capillary melting point apparatus and are uncorrected.

Infrared and Nuclear Magnetic Resonance Sepctra.—Infrared spectra were recorded with a Beckman Model IR-10 grating infrared spectrophotometer. The spectra of solids were obtained using KBr pellets and those of liquids by using KBr or NaCl disks. The proton magnetic resonance spectra were recorded with a Varian A-60 spectrometer. The spectra of liquids were run as pure samples and those of solids were determined in deuteriochloroform, deuterated acetone, or deuterated dimethyl sulfoxide with tetramethylsilane as internal standard. Infrared data of compounds not previously reported are listed.

Synthesis of Chloramines.—Dimethylchloramine was prepared by a procedure analogous to the Raschig synthesis of chloramine.[20] Chloramine was prepared in a generator by an anhydrous method developed by Mattair and Sisler[21] involving the gas-phase chlorination of ammonia.

The rates of flow of ammonia, nitrogen, and chlorine in the generator were 1.2, 0.3, and 0.1 mol/hr, respectively, and the production rate of chloramine was *ca.* 0.1 mol/hr. The ethereal solution of chloramine was freed from ammonia by the method of Gilson and Sisler[22] in which the chloramine solution is passed through a column of anhydrous copper sulfate.

Procedure for Chloramination Reactions.—The experimental procedures for most of the reactions studied were similar. The typical procedure consisted of adding dropwise chloramine solution or dimethylchloramine solution in dry diethyl ether to a solution of the mercaptan in dry diethyl ether with constant stirring. The temperature of the reaction mixture was kept at 25° except as otherwise stated. There was an immediate turbidity followed by the formation of a white precipitate, and dense white fumes were also observed. The reactions were generally exothermic. A water-cooled condenser and magnetic stirrer were used, and air and moisture were kept away using Drierite tubes. After the addition of chloramine was complete, the reaction mixture was stirred overnight, followed by refluxing for periods varying from 1 to 3 hr.

On filtration, generally a white solid was obtained which was dried under vacuum and was identified in most cases as ammonium chloride or dimethylammonium chloride, except in those cases where the disulfides formed are insoluble in diethyl ether.

Excess of mercaptan or chloramine, as the case may be, was removed from the ethereal filtrate. For removing excess mercaptan, fractional distillation or treatment with 2 *N* NaOH was carried out. Excess chloramine and ether could be easily removed under reduced pressure. The unused mercaptan was estimated by titration with an alcoholic solution of iodine containing small amounts of pyridine to remove the hydrogen iodide formed. The end point was the appearance of iodine color.[23] Chloramine and dimethylchloramine concentrations in reacting solutions were estimated iodometrically. To a measured volume (5 ml) of ethereal solution of chloramine, *ca.* 20–40 ml of 50% acetic acid was added followed by excess of potassium iodide. The iodine liberated was titrated against standard thiosulfate solution.

$$R_2'NCl + 2H^+ + 2I^- \xrightarrow{R' = H \text{ or } CH_3} R_2'NH_2^+ + I_2 + Cl^-$$

The products obtained were recrystallized from appropriate solvents. The purities of liquids were tested by vapor phase chromatography.

If, as we initially believed, chloramine reacts with mercaptans to form disulfides first, followed by cleavage of sulfur–sulfur bond to give $RSNH_2$ or $RSN(CH_3)_2$ and RSCl, the varying mole ratios of chloramine to mercaptan might have given different reaction products. With this point in view, extensive work was carried out with the chloraminations of cyclohexylmercaptan and of thiophenol using varying mole ratios. The results of these experiments are summarized in Table I.

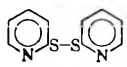
The mole ratios of mercaptans to chloramines in the reactions of 2-mercaptonaphthalene, 2-mercaptopyridine, 2-mercaptoethanol, and 1-butanethiol were kept at slightly in excess of 2:1. These results are summarized in Table II.

The preparations of mixed disulfides by chloramination of a mixture of thiols and the reaction of 1,2-ethanedithiol with dimethylchloramine have been carried out and are discussed separately. A number of experiments were carried out to obtain

(20) A. Berg, *Ann. Chim. Phys.*, **3**, 319 (1894).
(21) R. Mattair and H. H. Sisler, *J. Amer. Chem. Soc.*, **73**, 1619 (1951).
(22) I. T. Gilson and H. H. Sisler, *Inorg. Chem.*, **4**, 273 (1965).
(23) D. P. Harnish and D. A. Tarbell, *Anal. Chem.*, **21**, 968 (1949).

TABLE II

CHLORAMINATION REACTIONS WITH 2-MERCAPTONAPHTHALENE, 2-MERCAPTOPYRIDINE, 2-MERCAPTOETHANOL, AND 1-BUTANETHIOL IN DIETHYL ETHER (THIOL TO CHLORAMINE MOL RATIO > 2:1)

Reactants[a]			Mp or bp, °C	
A	B[b]	Products[c]	(mm)	Yield, %
$(CH_3)_2NCl$	2-Mercaptonaphthalene	β-$C_{10}H_7S$-S-β-$C_{10}H_7$[d]	135–136	70.6[e]
NH_2Cl (+ NH_3)	2-Mercaptonaphthalene	β-$C_{10}H_7S$-S-β-$C_{10}H_7$	135–136	94.3[e]
$(CH_3)_2NCl$	2-Mercaptopyridine[f]		52	77.6[e]
NH_2Cl (+ NH_3)	2-Mercaptopyridine		51–52	83.1[e]
$(CH_3)_2NCl$	2-Mercaptoethanol[h]	$HOCH_2CH_2S$–SCH_2CH_2OH[i]	25–26	47.6[j]
NH_2Cl (+ NH_3)	2-Mercaptoethanol	$HOCH_2CH_2S$–SCH_2CH_2OH	27–28	67.0[e]
			175–176 (4.5)	
$(CH_3)_2NCl$	1-Butanethiol	$CH_3(CH_2)_3S$–$S(CH_2)_3CH_3$[k]	73–74 (1.1)	80.7[e]
NH_2Cl (+ NH_3)	1-Butanethiol	$CH_3(CH_2)_3S$–$S(CH_2)_3CH_3$	76 (1.75)	74.9[e]

[a] A added dropwise to B. [b] Taken in slight excess of specified mole ratio. [c] Dimethylammonium chloride and ammonium chloride formed from $(CH_3)_2NCl$ and NH_2Cl, respectively, were obtained in almost quantitative yields. [d] Light yellow compound, insoluble in diethyl ether. [e] Based on chloramine. [f] Temperature of the reaction mixture was kept at 0–5°. [g] On evaporation of ether, a dark red, viscous liquid was left which turned into a light red-brown solid. [h] Temperature of the reaction mixture was kept at 10–15°. [i] Light yellow liquid with solid particles at 25° (room temperature). [j] Based on mercaptan used. [k] Colorless liquid, turning slightly yellow at higher temperature.

evidence concerning the reaction mechanism. Two of them are described under the heading "General Experiments," and are discussed later.

Chloramination of Mixtures of Thiols.—Using procedures analogous to those described, an equimolar mixture of 2-mercaptonaphthalene and thiophenol was treated with a less than equivalent amount of dimethylchloramine. An 80.6% yield of mixtures of diphenyl disulfide, di-β-naphthyl disulfide, and β-naphthylphenyl disulfide based on dimethylchloramine was obtained. The mole ratio of these disulfides in the mixed product was *ca.* 10.5:9.5:9.0, respectively. β-Naphthylphenyl disulfide, soluble in diethyl ether and obtained by fractional crystallization of absolute alcohol, is a white, crystalline solid melting at 73°. The ^1H nmr spectrum in acetone-d_6 gave a very broad complex peak in the aromatic region.

Anal. Calcd for $C_{16}H_{12}S_2$: C, 71.64; H, 4.48; S, 23.88. Found: C, 71.5; H, 4.57; S, 23.64.

A similar experiment with a mixture of thiophenol and 1-butanethiol gave an overall yield of a mixed disulfide product of 65%. The product contained di-*n*-butyl disulfide, diphenyl disulfide, and *n*-butylphenyl disulfide in a mole ratio of 7.0:7.0:10.0, respectively. Infrared data for the two mixed disulfides, not reported previously, are listed in Table III. *n*-Butylphenyl disulfide was a light yellow liquid, bp 115–118° (2.8 mm). The ^1H nmr spectrum confirms this identification.

TABLE III

INFRARED DATA[a]

β-$C_{10}H_7S$–SC_6H_5

400 vw, 475 m, 490 m, 605 w, 630 w, 645 vw, 690 s, 745 vs, 820 vs, 850–865 s, 890 sh, 900 m, 920 m, 948 m, 960 sh, 970 m, 1005 w, 1030 s, 1060 w, 1075 m, 1080 sh, 1105 vw, 1140 s, 1150 sh, 1185 vw, 1200 w, 1300 w, 1355 m, 1375 w, 1442 s, 1480 s, 1505 m, 1580 s, 1590 s, 1625 m, 1730 vw, 1860 vw, 2330 vw, 3060 w

$CH_3(CH_2)_3S$–SC_6H_5

695 s, 745 vs, 785 sh, 840 vw, 878 w, 910 sh, 920 w, 970 vw, 1005 w, 1030 s, 1072 m, 1080 sh, 1100 w, 1160 vw, 1182 w, 1225 m, 1268 m, 1304 m, 1330 vw, 1382 m, 1416 m, 1442 s, 1470 sh, 1480 s, 1585 s, 1630–1640 w, br, 1730 vw, 1790 w, 1850–65 w, br, 1940 w, 2880 s, 2935 vs, 2960 vs, 3020 sh, 3068 m

$(-CH_2CH_2S$–$S-)_n$ (?)

510 w, 585–590 w, br, 680 m, 738 s, 835–45 w, br, 890 vw, 1025 w, 1110 m, 1188 vs, 1250 m, 1340 sh, 1410 s, 1440 w, 1460–1470 w, br, 1610–1640 w, br, 2420 w, 2910 w, 3400–3430 w, br

[a] In cm^{-1}. Abbreviations: s, strong; m, medium; w, weak; br, broad; v, very; sh, shoulder.

Anal. Calcd for $C_{10}H_{14}S_2$: C, 60.6; H, 7.07; S, 32.32. Found: C, 60.75; H, 7.19; S, 32.17.

Reaction of 1,2-Ethanedithiol with Dimethylchloramine.—A 30-ml portion (24.6 mmol) of 0.82 *M* dimethylchloramine solution in diethyl ether was added dropwise to a solution of 5 g (53.2 mmol) of 1,2-ethanedithiol in 100 ml of dry ether taken in a 250-ml, round-bottom flask. There was an immediate white precipitate. After all the addition of chloramine was complete, the reaction mixture was stirred for 24 hr followed by refluxing for 1 hr. White solid, 2.8 g, was obtained on filtration. Dimethylammonium chloride, was separated from it using absolute alcohol, in which it is soluble. A white, amorphous residue, 1.6 g (i), was left. Analysis of i showed that its composition is represented by $(CH_2S)_n$. The infrared spectral data, as shown in Table III, show evidence of $-CH_2S$ and S–S linkages in i. This substance shrinks at 122–128°, becomes a pasty, viscous, brown mass at 133°, changes color to dark brown and then to reddish brown in the range 165–230°, and melts completely to give dark red liquid at 248°. At 255–260° it gives dark red particles and a yellow sublimate condenses on the upper side of the capillary. Compound i is insoluble in water, benzene, acetone, carbon disulfide, alcohol, chloroform, dioxane, ether, acetonitrile, dimethyl sulfoxide, dimethylformamide, etc. The mass spectrum of i shows well-defined peaks at *m/e* 184, 217, and 229.

Anal. Calcd for CH_2S: C, 26.08; H, 4.34; S, 69.56. Found: C, 26.26; H, 4.69; S, 68.53.

General Experiments. A.—The reaction of benzenethiol and dimethylchloramine in ether (mol ratio 2:1) was carried out in the dark, using the same general procedure as described earlier. Immediately after the addition of dimethylchloramine was complete, the solution was filtered. A white precipitate was retained on the filter and was identified as dimethylammonium chloride. On evaporating the ether, a yellow-white residue was left which was found to be diphenyl disulfide.

B.—Diphenyl disulfide and di-*n*-butyl disulfide were separately treated, under nitrogen atmosphere, with an excess of dimethylchloramine, keeping air and moisture away as far as possible. Prolonged stirring and refluxing produced no sulfenamide derivatives of the type $RSN(CH_3)_2$ or $RSNH_2$. It was concluded that cleavage of sulfur–sulfur bonds does not occur by action of chloramines over disulfides. The starting materials in all cases were almost quantitatively recovered.

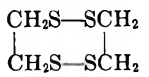
Results and Discussion

The infrared spectra for the products reported in this study are quite in accordance with their formulation as disulfides of the type RSSR.

The only previous references to the formation of a disulfide by oxidation of 1,2-ethanedithiol are two very old reports of its reaction with halogens.[24,25]

(24) R. Otto and A. Rössing, *Chem. Ber.*, **19**, 2079 (1886).
(25) H. Fasbender, *ibid.*, **21**, 1470 (1888).

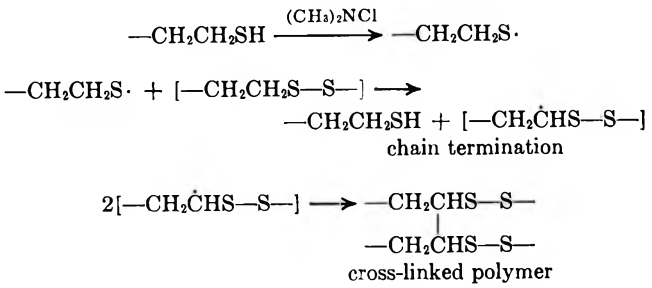
The structure proposed in these reports for the resulting compound is depicted below.



These experiments were repeated using an alcoholic solution of iodine containing 1% pyridine to remove the HI formed and the compound so obtained was identical with compound i described in the Experimental Section. It is clear that this cyclic structure does not correspond to the physical and chemical properties of our product i or those of the product of the earlier reported reaction.[24,25]

If the structure is that of a linear polymer of the type $[-CH_2CH_2-S-S-]_n$, the compound should have been soluble in good polymer solvents such as N-methylpyrolidone, hexafluoroisopropyl alcohol, and hexamethylphosphoramide. It was observed that compound i is insoluble in these solvents even on prolonged stirring. It was also not possible to obtain the simple cyclic disulfide proposed[24,25] by heating i to *ca.* 200° in a semimicro sublimation apparatus and trying to condense the product on a cold finger.

It is suggested that cross linking could have been produced by a mechanism such as the following.



Such a cross-linked polymer would be expected to behave in accordance with our observations for product i.

On the basis of the facts that our chloramination reactions yielded disulfides only, but no sulfenamides [$RSNH_2$ or $RSN(CH_3)_2$] or sulfenyl chlorides (RSCl), as reported in the literature,[14-18,26,27] that the conditions of the reactions and the lack of a probable initiator were not favorable for free radical formation, that the reactions proceeded rapidly in the dark, and that we have shown that the sulfur–sulfur bonds of the disulfides are not subject to cleavage by chloramines, we believe the most probable reaction path for the chloraminations of thiols in ether to be as follows.

$$RSH + R_2'NCl \xrightarrow{R' = H \text{ or } CH_3} RSNR_2' + HCl \quad (1)$$

$$RSNR_2' + RSH \xrightarrow{\text{fast}} RSSR + R_2'NH \quad (2)$$

or

$$RSNR_2' + HCl \xrightarrow{\text{fast}} RSCl + R_2'NH$$

$$RSCl + RSH \xrightarrow{\text{fast}} RSSR + HCl$$

$$R_2'NH + HCl \longrightarrow R_2'NH_2Cl \quad (3)$$

The failure to isolate the sulfenamides ($RSNR_2'$) probably results from their reactivity toward HCl and toward thiols combined with their solubility in ether. Earlier references[14-18] to the formation of sulfenamides by reactions of chloramines with alkali mercaptides involved experiments in aqueous systems in which sulfenamides are insoluble.

Registry No.—Thiophenol, 108-98-5; cyclohexylmercaptan, 1569-69-3; 2-mercaptonaphthalene, 91-60-1; 2-mercaptopyridine, 2637-34-5; 2-mercaptoethanol, 60-24-2; 1-butanethiol, 109-79-5; β-naphthylphenyl disulfide, 23853-95-4; *n*-butylphenyl disulfide, 20129-23-1.

Acknowledgment.—We are pleased to gratefully acknowledge the support of this research by the National Science Foundation through Research Project GP-4505 with the University of Florida.

(26) J. B. Billman, J. Garrison, R. Anderson, and B. Wolnak, *J. Amer. Chem. Soc.*, **63**, 1920 (1941).
(27) Reference 19, pp 265, 269, 274.

Radical Coupling Products from the Permanganate Oxidation of N-Phenyl-2-naphthylamine

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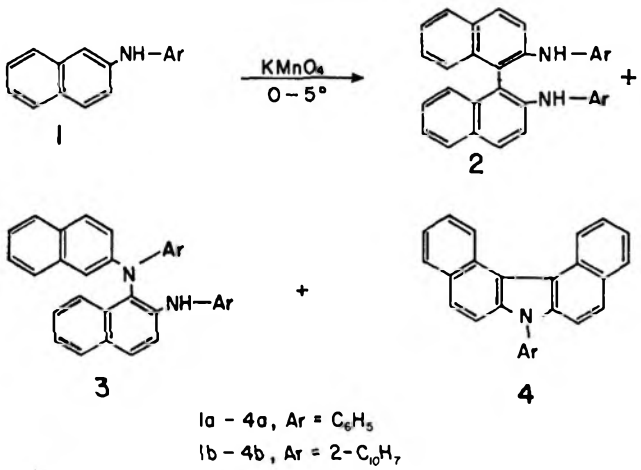
The oxidative dimerization of N-phenyl-2-naphthylamine by neutral potassium permanganate results in the formation of coupling products **2** and **3**, with the dibenzocarbazole **4** as a minor product. The structures of **2** and **4** were reported earlier. The structure of **3** has now been confirmed by the synthesis of the N-phenyl derivative from a known 1,2-disubstituted naphthalene compound. The product distribution from the permanganate oxidation is the same as that from the coupling of amino radicals generated from the appropriate tetrazene. The effects of substituents on the permanganate oxidation of N-aryl-2-naphthylamines are correlated by σ^+ to give a ρ of -0.68. These results are consistent with a mechanism involving hydrogen transfer to permanganate followed by product formation *via* carbon–carbon and carbon–nitrogen coupling of the resulting amino radicals.

Recently we reported[1] the products arising from the oxidation of N-phenyl-2-naphthylamine by neutral potassium permanganate in acetone (Scheme I).

SCHEME I



In contrast to the oxidation of diphenylamine,[2] no tetrasubstituted hydrazine was detected. In the present paper we wish to confirm the tentative structural assignment of **3a** made earlier, and present additional results bearing on the mechanism of the reaction.

Results

The structures of **2a** and **4a** have been definitely assigned.[1] The carbon–nitrogen coupled product, **3a**, was tentatively assigned the semidine structure on the basis of elemental analysis, molecular weight, and the determination of one N–H bond per molecule. The chemical shift of the amino hydrogen of **3a** was 0.74 ppm downfield from that of **1a**, suggesting an *ortho* diamine structure.

As mentioned earlier,[1] the most direct synthesis of **3a** should be afforded by the Ullmann reaction between **1a** and 1-iodo-N-phenyl-2-naphthylamine. The iodo compound could not be prepared, however. Attempts to treat iodine or iodine monochloride with **1a** under a variety of conditions led to intractable tars. The reaction of iodine monochloride with the N-acetyl derivative of **1a** in acetic acid[3] resulted in an addition compound.

Since the iodo compound was unavailable, the N-phenyl derivative of **3a** was prepared from a known *ortho*-substituted naphthalene compound (**5**) as shown in Scheme II. The reaction of **3a** with iodobenzene and copper gave N-(2-naphthyl)-N,N′,N′-triphenyl-1,2-naphthylenediamine (**9**), which was identical with that prepared from 2-amino-1-nitronaphthalene *via* the route shown in Scheme II. These results confirm the earlier assignment of the semidine structure to N-(2-naphthyl)-N,N′-diphenyl-1,2-naphthylenediamine (**3a**).[4]

N-Aryl-2-naphthylamines with substituents in the benzene ring were oxidized by permanganate in the same manner as **1a**. The carbon–carbon coupling products (**2c–2g**) were isolated in the crystalline state and each was characterized by molecular weight, analysis, and the presence of two secondary N–H bonds per molecule. Results are summarized in Table I. The predominant fragmentation in the mass spectrum of each oxidative dimer was the extrusion of an arylamino moiety, analogous to the chemical degradation reported for **2a**.[1] Although the thin layer chromatograms of reaction mixtures indicated that semidines **3c–3g** were formed, none was isolated in crystalline form. The amorphous semidine fraction, **3d**, from the oxidation of **1d** was isolated by column chromatography. Its infrared spectrum was consistent with the assigned structure and showed one N–H bond per molecule. Attempts to induce crystallization have been unsuccessful. The difficulty of obtaining crystalline forms of **3a** and **3b** has been discussed.[1]

Competitive oxidations of N-aryl-2-naphthylamines were conducted by allowing mixtures of two amines to

$$A + KMnO_4 \xrightarrow{k_A} \text{products} \quad (1)$$

$$B + KMnO_4 \xrightarrow{k_B} \text{products} \quad (2)$$

compete for a deficient quantity of potassium permanganate in acetone at 0° (eq 1, 2).

(1) R. F. Bridger, D. A. Law, D. F. Bowman, B. S. Middleton, and K. U. Ingold, *J. Org. Chem.*, **33**, 4329 (1968).

(2) (a) H. Wieland and S. Gambarjan, *Chem. Ber.*, **39**, 1499 (1906); (b) H. Wieland, *Justus Liebigs Ann. Chem.*, **381**, 200 (1911).

(3) This procedure has been reported successful in the preparation of 1-iodo-2-acetamidonaphthalene: H. Willstaedt and G. Scheiber, *Chem. Ber.*, **67**, 466 (1934).

(4) See ref 1 for a discussion of the incorrect assignments of structure **3** to **2a** and **2b** by previous workers.

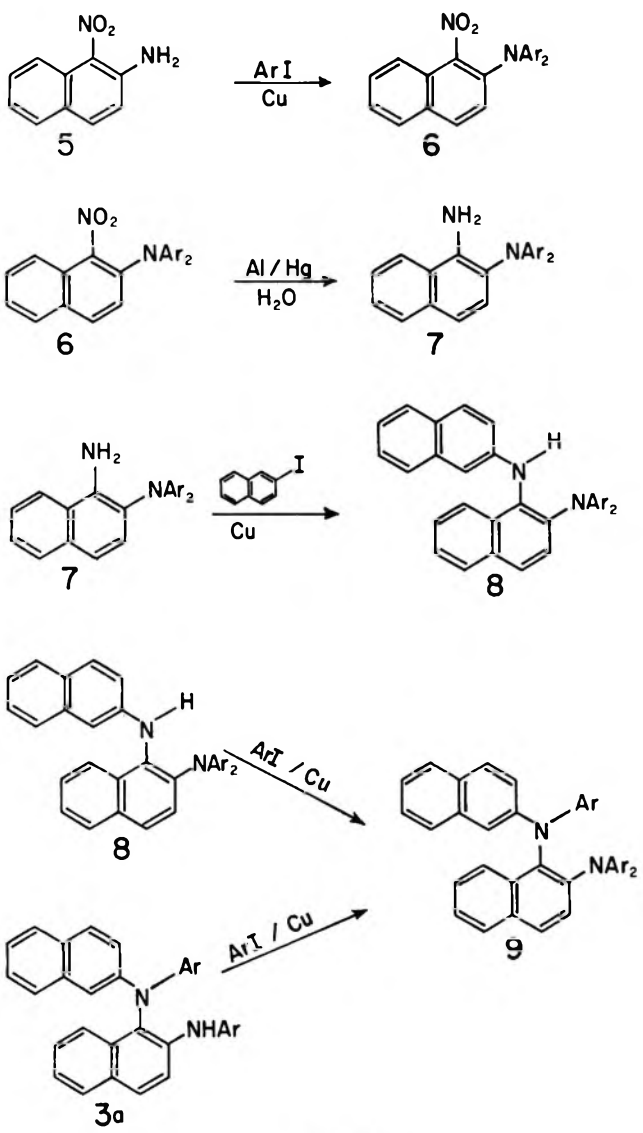
TABLE I

PROPERTIES OF 1,1'-BIS(N-ARYL-2-NAPHTHYLAMINES)

Compd[a]	Ar	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Infrared spectra[b] NH (2), cm⁻¹	NH (1), cm⁻¹	$\epsilon_{NH\ (2)}/\epsilon_{NH\ (1)}$[b]	Yield, %
2c	*m*-$CH_3OC_6H_4$	182–183	82.23	5.68	5.64	82.53	5.75	5.57	3405	3440	2.0	23
2d	*p*-$CH_3OC_6H_4$	240–241	82.23	5.68	5.64	82.31	5.74	5.62	3405	3420	1.9	44
2e	*m*-$CH_3C_6H_4$	167–168	87.89	6.07	6.03	87.89	6.07	6.08	3410	3435	2.1	22
2f	*p*-$CH_3C_6H_4$	229–230[c]	87.89	6.07	6.03	87.82	6.11	5.98	3405	3435	2.1	24
2g	*m*-ClC_6H_4[d]	177–178	76.04	4.39	5.54	76.08	4.47	5.49	3405	3435	1.9	31

[a] Mass spectra of all compounds gave correct molecular weights. [b] 1.4% (w/v) in $CDCl_3$. See ref 1. [c] Another form with mp 208–210° was observed when first isolated. [d] Calcd: Cl, 14.03. Found: Cl, 14.10.

SCHEME II



When the ratio of the rates of disappearance of a pair of competing amines, A and B, was taken, the permanganate concentrations cancel and the relative reactivity is given by eq 3.

$$\frac{k_B}{k_A} = \frac{\log[B]_0/[B]}{\log[A]_0/[A]} \qquad (3)$$

The validity of eq 3 was tested by changing amine concentration and extent of oxidation and by comparing relative reactivities cross-calculated from different pairs of reactants. Results are summarized in Table II.

TABLE II

COMPETITIVE OXIDATIONS OF N-ARYL-2-NAPHTHYLAMINES BY POTASSIUM PERMANGANATE AT 0°

Amine[a] (concn, *M*) A	Amine[a] (concn, *M*) B	Conversion, %	k_B/k_A
1a (0.3)	**1c** (0.3)	38	0.90
1a (0.4)	**1d** (0.2)	41	3.15
1a (0.3)	**1e** (0.3)	17	1.23
1a (0.3)	**1e** (0.3)	32	1.19
1a (0.4)	**1e** (0.2)	39	1.24
1a (0.4)	**1f** (0.2)	48	1.58
1a (0.3)	**1g** (0.3)	39	0.53
1e (0.3)	**1c** (0.3)	43	0.72 (*vs.* 0.73)[b]
1f (0.4)	**1d** (0.2)	45	2.24 (*vs.* 2.0)[b]

[a] Substituents on C_6H_4X: **a**, H; **c**, *m*-OCH_3; **d**, *p*-OCH_3; **e**, *m*-CH_3; **f**, *p*-CH_3; **g**, *m*-Cl. [b] Calculated from reactivities of each component relative to **1a**.

Discussion

There are several reasons for considering the mechanism of the permanganate oxidation of **1**. General knowledge of diarylamino radicals is surprisingly meager. Recent investigations reveal that these radicals are not particularly stable toward coupling and disproportionation reactions.[5–7] The few examples of stable diarylamino radicals which have been unambiguously identified by esr show that electron-donating *para* substituents are necessary.[5] Since the classic work of Wieland and coworkers, there has been little activity in the oxidation of secondary aromatic amines by permanganate in neutral solution. Most of the quantitative information available deals with other substrates in acidic or basic media.[8] The formation of tetraphenyl hydrazine from the oxidation of diphenylamine seems best explained by the coupling of neutral radicals (eq 4), though the dimer–monomer equilibrium

$$2Ph_2N\cdot \longrightarrow Ph_2N\text{–}NPh_2 \qquad (4)$$

suggested by Wieland[2] is not detectable except in the special cases mentioned above.[5] In the naphthyl series, however, the hydrazine is not a product.[1] While the products are those expected of radical cou-

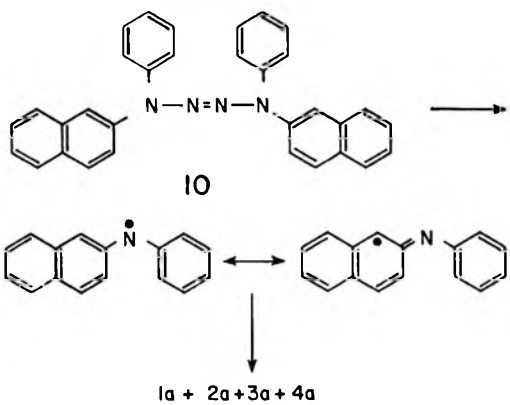
(5) F. A. Neugebauer and P. H. H. Fischer, *Chem. Ber.*, **98**, 844 (1965).
(6) H. Musso, *ibid.*, **92**, 2881 (1959).
(7) K. M. Johnston, G. H. Williams, and H. J. Williams, *J. Chem. Soc., B*, 1114 (1966).
(8) R. Stewart in "Oxidation in Organic Chemistry," Part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, Chapter 1.

pling reactions, both carbon–carbon[9–12] and carbon–nitrogen[13] coupled products have been isolated from oxidations of other amines proceeding *via* radical cation intermediates which were identified by esr.

A detailed kinetic study of the permanganate oxidation in acetone is impracticable because the medium is constantly changing during the course of the reaction. It is possible, however, to probe the initial reaction by measuring the effects of substituents from competitive experiments. The nature of the intermediates involved in product formation can be defined by comparing the products of permanganate oxidation with those from an independent source of amino radicals. The oxidation of **1** is well suited for this approach, as the products[1] are well defined and stable toward oxidation, and no significant quantities of disproportionation[6] products or oligomers are formed.

N-Phenyl-2-naphthylamino radicals were generated by the photolysis and thermolysis of 1,4-diphenyl-1,4-di(2-naphthyl)-2-tetrazene (**10**), as shown in Scheme III. Photolysis and thermolysis of the tetrazene gave

SCHEME III



essentially the same results. Products from the decomposition of **10** are compared with those of the permanganate oxidation of **1a** in Table III. The relative amounts of **2a** and **3a** from the two reactions are the same within experimental error, and only minor variations were observed in the yields of **4a**. While this work was in progress, Waters and White[14] reported a similar study of the oxidation of carbazole. Although the complexity of the reaction mixture precluded quantitative comparison, their qualitative results agree with the present findings.

The formation of substantial quantities of **1a** from the decomposition of **10** was not expected. This is of interest in connection with the stoichiometry of permanganate oxidation of amines. Experimentally the stoichiometry of eq 5 is usually not observed and con-

$$6\mathrm{ArNHPh} + 2\mathrm{KMnO_4} \longrightarrow 3(\mathrm{ArNPh})_2 + 2\mathrm{MnO_2} + 2\mathrm{KOH} + 2\mathrm{H_2O} \quad (5)$$

siderable amounts of starting material are recovered, even though all of the permanganate is consumed.

TABLE III

COMPARISON OF PRODUCTS FROM PERMANGANATE OXIDATION AND TETRAZENE DECOMPOSITION

Compd	Yield, % Permanganate reaction[a]	Tetrazene photolysis[b]	Tetrazene thermolysis[c]
1a	25 ± 1[d]	16 ± 1[e]	15 ± 1[e]
2a	36 ± 2[f]	35 ± 2	33 ± 2
3a	24 ± 1[f]	25 ± 1	25 ± 1
4a	0.4[f]	1.0	2.8
Ratio, **2a** to **3a**	1.5 ± 0.2	1.4 ± 0.2	1.3 ± 0.2

[a] In acetone at 0–5°, initially 0.5 *M* **1a**. [b] In acetone at 5°, 0.02 *M* **10**. [c] In acetone at 40°, 0.02 *M* **10**. [d] Error limits represent range of duplicate experiments. [e] Mol/200 mol of **10**. [f] Mol/50 mol of **1a**.

The obvious explanation that compound **1a** is formed by a hydrogen-transfer reaction (eq 6) must be

$$\mathrm{ArNPh} + \mathrm{CH_3CCH_3}\ (\mathrm{O}) \not\longrightarrow \mathrm{ArNHPh.} + \cdot\mathrm{CH_2CCH_3}\ (\mathrm{O}) \quad (6)$$

rejected because the formation of **1a** from **10** is independent of temperature (*i.e.*, no apparent activation energy) and fails to exhibit a primary deuterium isotope effect, as shown in Table IV. Since **1a** is formed in

TABLE IV

DECOMPOSITION OF TETRAZENE **10** IN ACETONE AND ACETONE-d_6

Solvent	Conditions (temp, °C)	Yield[a] of **1a**
Acetone	Thermolysis (25)	19
Acetone-d_6	Thermolysis (25)	19
Acetone	Thermolysis (56)	16
Acetone-d_6	Thermolysis (56)	15
Acetone	Photolysis (5)	16
Acetone-d_6	Photolysis (5)	17

[a] Mol/200 mol of **10**.

5–10% yields from the decomposition of **10** in solvents which are poor hydrogen donors,[15] we must conclude that its formation is a property of N-aryl-2-naphthylamino radicals or of the tetrazene. Deviations from the stoichiometry of eq 5 most likely occur by oxidation of acetone, especially in the later stages of the reaction as base accumulates. Drummond and Waters[16] have reported that the consumption of permanganate by acetone under basic conditions can be quite high. The well-known precautions[2] of purifying the acetone and adding permanganate slowly do not always ensure good conversion of amine. We have observed that the amine concentration is an important variable also. At low concentrations (0.15 *M*) of **1**, very little amine is converted in spite of fairly rapid consumption of permanganate. At amine concentrations of 0.5 *M* or higher, the reaction proceeds normally, indicating competition between amine and solvent for the permanganate.

The quantitative agreement between the products of the tetrazene decomposition and those of the permanganate oxidation (Table III) establishes that the oxidation products of **1a** are formed by coupling of amino radicals, as shown in Scheme III. The competitive oxidations of Table II show that the rates of disappear-

(9) R. F. Nelson and R. N. Adams, *J. Amer. Chem. Soc.*, **90**, 3925 (1968).
(10) E. T. Seo, R. F. Nelson, J. M. Fritsch, L. S. Marcoux, D. W. Leedy, and R. M. Adams, *ibid.*, **88**, 3498 (1966).
(11) D. H. Iles and A. Ledwith, *Chem. Commun.*, 498 (1968).
(12) D. L. Allara, B. C. Gilbert, and R. O. C. Norman, *ibid.*, 319 (1965).
(13) Y. Tsujino, *Tetrahedron Lett.*, 763 (1969).
(14) W. A. Waters and J. E. White, *J. Chem. Soc., C*, 740 (1968).
(15) Unpublished results from this laboratory; a detailed investigation of the decomposition of tetrazene **10** is in progress and will be reported soon.
(16) A. Y. Drummond and W. A. Waters, *J. Chem. Soc.*, 435 (1953).

ance of amine are not strongly influenced by substituents. These data follow a Hammett relationship, correlating well with σ^+. The plot in Figure 1 has a slope of -0.68. While the magnitude of ρ may be attenuated somewhat by the naphthyl group, it indicates that reaction is at the amino group. The observed value of ρ is in the range expected for a free-radical hydrogen-transfer reaction. Values of ρ for reactions of alkoxy and peroxy radicals with a variety of substrates fall in the range -0.4 to -1.5.[17] Brownlie and Ingold[18] have reported substituent effects in the reaction of peroxy radicals with diphenylamines at 65° to give a ρ of -0.89, correlated with σ^+. The σ^+ correlation implies significant polar contributions to the transition state for hydrogen removal, as has been demonstrated for a variety of free-radical reactions.[18,19] Since formation of the hydroxyl radical[20] is unlikely[16,21] in weakly basic or neutral solution, the permanganate ion seems the most probable hydrogen abstraction reactant.

Experimentally, a rigorous distinction cannot be made between a hydrogen atom transfer and a two-step sequence involving electron transfer at nitrogen, followed by rapid loss of a proton to oxyanion or some other base[22] (eq 7, 8). It is probable that reaction 8

$$>NH + MnO_4^- \longrightarrow >N\cdot + MHnO_4^- \quad (7)$$

$$>NH + MnO_4^- \longrightarrow >\dot{N}H^+ MnO_4^{2-} \quad (8a)$$

$$>\dot{N}H^+ + MnO_4^{2-}(OH^-) \longrightarrow >N\cdot + MHnO_4^-(H_2O) \quad (8b)$$

would exhibit a substituent effect much larger than that observed experimentally. If a radical cation is involved, its lifetime is insufficient to have any effect on product formation.

An alternative mechanism would involve electron transfer from the aromatic nucleus, such as is operative in the cobalt(III) oxidation of aromatic hydrocarbons.[23] This type of reaction, however, is characterized by a much higher ρ value (-2.4 at 65°). The good fit observed with methoxy substituents discounts a change of mechanism with substituent. Nave and Trahanovsky[24] observed both *m*- and *p*-methoxy to be greatly enhanced in reactions of cerium(IV) which change to a π-electron-transfer mechanism in the presence of strongly electron-donating substituents.

In summary, the oxidation of **1** may be described as originating in a hydrogen transfer from the amino group to permanganate, followed by coupling of amino radicals to products. The initial oxidation of amine by permanganate produces manganate ion (or its conjugate acid), which is known to disproportionate[25] rapidly in neutral or weakly basic media to permanganate and manganese dioxide.

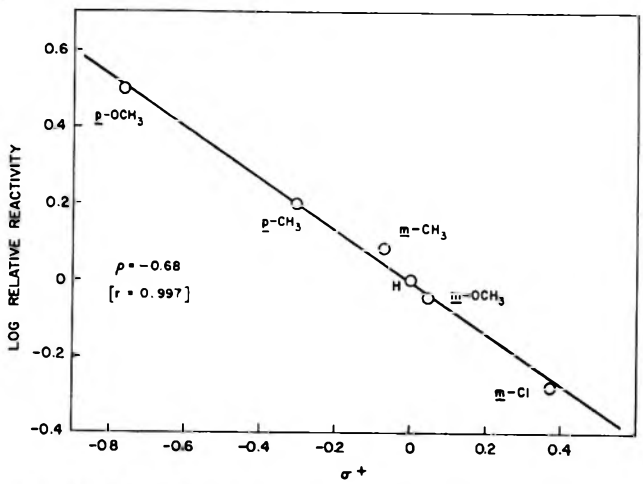


Figure 1.—Effects of substituents on the oxidation of N-phenyl-2-naphthylamine by potassium permanganate.

$$6ArNHPh + 6MnO_4^- \longrightarrow 6Ar\dot{N}Ph + 6HMnO_4^- \quad (9)$$

$$6Ar\dot{N}Ph \longrightarrow 3(ArNPh)_2 \text{ (Scheme I)} \quad (10)$$

$$6HMnO_4^- \longrightarrow 4MnO_4^- + 2MnO_2 + 2H_2O + 2OH^- \quad (11)$$

Experimental Section

Analytical Methods.—Compounds **1a**, **2a**, and (**3a** + **4a**) were separated on silica gel sheets of 100-μ thickness (Eastman "Chromagram") by developing in carbon tetrachloride. Compound **4a** was completely resolved on a thicker (250-μ) silica layer (Brinkmann). After visualization with ultraviolet light, spots or streaks were removed and treated twice (20 min) with boiling ethanol. Samples were diluted to a known volume, and concentrations were determined by ultraviolet absorption at 305 nm for compounds **1a**–**3a** and 365 nm for **4a**. Gas chromatography[1] was used as an independent method for **1a**, which was sometimes incompletely resolved from **2a**. Compounds **1a** and **1c**–**1g** were determined in reaction mixtures by glpc with a 10-ft silicone rubber column, using *m*-diphenoxybenzene as an internal standard.

The nmr method employed earlier[1] was found unreliable for quantitative purposes. Broadening of the N–H absorption of **3a** in some reaction mixtures made accurate integration difficult. This is believed to be due to impurities in the reaction mixture, possibly oxidation products of acetone.

Materials.—Preparations of **1a**–**4a** have been described.[1] N-Aryl-2-naphthylamines **1c**–**1g** were prepared by the iodine-catalyzed reactions of the appropriate anilines with 2-naphthol.[26] Melting points agreed with literature values, and ultraviolet and nmr spectra confirmed structures. Contrary to the original reference, extensive dehydrochlorination took place during the reaction of *p*-chloroaniline with 2-naphthol; the only product isolated was **1a**.

2-Amino-1-nitronaphthalene (**5**), mp 126–127°, was used as received from Aldrich Chemical Co., Inc. Other materials are described below. Conditions for the copper-catalyzed arylation of amino groups have been described.[1] Anhydrous potassium carbonate was employed as the base for these reactions. Changes in solvent or reaction time are noted where appropriate.

1-Nitro-N,N-diphenyl-2-naphthylamine (**6**).—The copper-catalyzed reaction of **5** (10 g, 0.053 mol) with excess iodobenzene (110 ml) serving as solvent yielded 12 g of crude product. Chromatography over alumina and recrystallization from diethyl ether produced 8.69 g (48% yield) of red, crystalline **6**, mp 153.5–154.5°. The infrared spectrum showed no NH absorption.

Anal. Calcd for $C_{22}H_{16}O_2N_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.69; H, 4.78; N, 8.03.

(17) See G. A. Russell and R. C. Williamson, Jr., *J. Amer. Chem. Soc.*, **86**, 2357 (1964), and references cited therein.

(18) I. T. Brownlie and K. U. Ingold, *Can. J. Chem.*, **45**, 2419 (1967).

(19) (a) G. A. Russell, *J. Amer. Chem. Soc.*, **78**, 1047 (1956); (b) G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958); (c) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **41**, 1744, 2800 (1963).

(20) (a) M. C. R. Symons, *J. Chem. Soc.*, 3956 (1953); (b) J. Kenyon and M. C. R. Symons, *ibid.*, 3580 (1953); (c) A. Schlund and H. Wendt, *Ber. Bunsenges. Phys. Chem.*, **72**, 649 (1968).

(21) W. A. Waters, *Quart. Rev.* (London), **12**, 277 (1958).

(22) The two-step sequence has been considered in the reactions of organic free radicals and atoms; grounds for its rejection are given by G. A. Russell, *Tetrahedron*, **8**, 101 (1959). The behavior of permanganate is too different from organic free radicals to include it categorically in these arguments.

(23) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14** (2), A-44 (1969).

(24) P. M. Nave and W. S. Trahanovsky, *J. Amer. Chem. Soc.*, **90**, 4755 (1968).

(25) Reference 8, p 2.

(26) E. Knoevenagel, *J. Prakt. Chem.*, [2] **89**, 1 (1914).

N',N'-Diphenyl-1,2-naphthylenediamine (7).—A solution of **6** (4 g, 11.8 mmol) in 200 ml of diethyl ether was added alternately with small portions of water (1 ml total) to 4 g of aluminum amalgam[27] during 1 hr at room temperature. The solution was stirred for an additional 1 hr, filtered, and dried over K_2CO_3. The product was eluted from alumina with diethyl ether and recrystallized from the same solvent to give 1.88 g (51% yield) of colorless **7**, mp 171–172°. The infrared spectrum showed NH absorptions at 3405 and 3490 cm^{-1}.

Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.84; N, 9.03. Found: C, 85.29; H, 5.90; N, 9.04.

N-(2-Naphthyl)-N',N'-diphenyl-1,2-naphthylenediamine (8).—This compound was prepared by the copper-catalyzed reaction of 1 g (3.22 mmol) of **7** with 0.818 g (3.22 mmol) of 2-iodonaphthalene. *n*-Dodecane was used as solvent, and reaction time was 6 hr at 200°. After distillation of the solvent under a stream of nitrogen, the crude product was eluted from alumina with benzene to give 0.9 g of a pale yellow glassy solid. The thin layer chromatogram showed that only a small amount (*ca.* 5%) of diarylation had occurred. The product was reluctant to crystallize, and seed crystals were obtained by allowing the glassy solid to stand under absolute ethanol at room temperature for 6 weeks. Crystallization of the main lot from ether–alcohol yielded 0.477 (34% yield) of **8**, mp 130–130.5°. The NH absorption at 3400 cm^{-1} had the intensity required for one NH bond per molecule.[1]

Anal. Calcd for $C_{32}H_{24}N_2$: C, 88.04; H, 5.54; N, 6.42. Found: C, 87.97; H, 5.60; N, 6.36.

N-(2-Naphthyl)-N,N',N'-triphenyl-1,2-naphthylenediamine (9).—The copper-catalyzed reaction of **8** (0.834 g, 1.91 mmol) with excess iodobenzene (10 ml) as solvent yielded after chromatography 0.824 g of pale yellow glassy solid, which crystallized within 1 hr upon addition of diethyl ether. Recrystallization from diethyl ether afforded 0.584 g (59% yield) of **9**, mp 205–207°. No NH absorption was observed in the infrared spectrum.

Anal. Calcd for $C_{38}H_{28}N_2$: C, 89.03; H, 5.50; N, 5.47. Found: C, 89.35; H, 5.44; N, 5.50.

Reaction of N-(2-Naphthyl)-N,N'-diphenyl-1,2-naphthylenediamine (3a) with Iodobenzene.—Under the conditions described above, **3a** (1 g, 2.3 mmol) reacted with iodobenzene to give 0.627 g (53% yield) of recrystallized **9**, mp 207–208.5°, mmp 205–208°. The infrared spectrum was identical with that of the authentic sample described above.

1,4-Diphenyl-1,4-di(2-naphthyl)-2-tetrazene (10).—A solution of potassium permanganate (2.69 g, 0.017 mol) in 500 ml of acetone was added dropwise during 3 hr to an acetone (100 ml) solution of 1-phenyl-1-(2-naphthyl)hydrazine[28] (6 g, 0.0256 mol) cooled in a Dry Ice–acetone bath under nitrogen. Stirring was continued at −78° for an additional 1 hr. The reaction was allowed to warm to 5° and filtered. The filtrate was evaporated to 60 ml at reduced pressure, stored at −18° for 16 hr, and filtered to give 3.72 g (62% yield) of tetrazene **10** as a rust-colored powder. The crude tetrazene was recrystallized with minimum decomposition by dissolving in boiling it methylene chloride (30 ml), adding absolute ethanol (25 ml) gradually, and cooling. Recovery of the pale yellow product was 70–80%. Decomposition points at several heating rates were determined with a Du Pont 900 differential thermal analyzer (deg/min, decomposition point): 2, 101; 5, 107; 10, 111; 30, 114. The decompositions of solid samples were strongly exothermic and those at fast heating rates appeared to be explosive. Thermolysis in solution was controlled and yielded 99 ± 1% of the theoretical azo nitrogen. The infrared spectrum showed a complete absence of NH bonds in the recrystallized product; uv max (2% CH_3CN–98% C_2H_5OH)[29] 350 nm (ϵ 2.22 × 10^4), 316 (1.9 × 10^4), and 274 (2.36 × 10^4).

Anal. Calcd for $C_{32}H_{24}N_4$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.62; H, 5.24; N, 11.95.

Photolysis of **10** was conducted under nitrogen in a quartz reactor with 2537-Å light for 10 hr at 5°. Nitrogen evolution was 93% of theory.

Registry No.—**1a**, 135-88-6; **2c**, 23854-07-1; **2d**, 23854-08-2; **2e**, 23854-09-3; **2f**, 23854-10-6; **2g**, 23854-11-7; **6**, 23854-12-8; **7**, 23854-13-9; **8**, 23854-14-0; **9**, 23890-44-0; **10**, 23854-15-1.

(27) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 20.

(28) J. Heidt, E. Gömbös, and F. Tudös, *KFKI (Közp. Fiz. Kut. Intez. Közlem.)*, **14**, 183 (1966).

(29) Acetonitrile was used to rapidly dissolve the tetrazene before dilution with alcohol in order to avoid decomposition from prolonged stirring.

The Oxidative Coupling Reaction of Vinylidenebisdialkylamines[1]

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A series of vinylidinebisdialkylamines, $R_2C{=}C(NMe_2)_2$, were oxidized by silver ion in acetonitrile solvent, yielding diamidinium salts *via* dimerization. Cyclization is also possible by this method, which is believed to involve radical cation intermediates.

While enamines and related compounds have been the focus of extensive research in recent years, rather limited attention has been paid to their oxidation.[2–7] We felt that vinylidenebisdialkylamines (ketene-N,N-acetals), a somewhat less common class of enamines, would be ideally suited as substrates for oxidation. It is, of course, well known that olefinic systems having electron-withdrawing substituents will reductively accept electrons, giving rise to subsequent reactions.[8] It seemed reasonable to assume that enamines would readily give up electrons to form reactive intermediates.

Results and Discussion

The observation that led to the present study was that 9-[bis(dimethylamino)methylene]fluorene (**1**) gradually turned blue on exposure to air and that the blue material was esr active. Bromine vapors caused the same transformation even more rapidly, and the oxidizing system settled on as the most convenient and free of side reactions was silver nitrate in acetonitrile.

Oxidation of **1** with silver nitrate produces a deep blue, esr active[9] solution of radical cation, which can be isolated as a copper-colored crystalline hexafluorophosphate, **2**. Although **1** and **2** can be reversibly interconverted electrochemically[9] in what appears to

(1) Reported in part by H. Weingarten and J. S. Wager, *Tetrahedron Lett.*, No. 38, 3267 (1969).

(2) F. A. Bell, R. A. Crellin, H. Fujii, and A. Ledwith, *Chem. Commun.*, 251 (1969).

(3) M. E. Kuehne and T. J. Giacobbe, *J. Org. Chem.*, **33**, 3359 (1968).

(4) F. Bohlmann and H. Peter, *Chem. Ber.*, **99**, 3362 (1966).

(5) V. Van Rheenen, *Chem. Commun.*, 314 (1969).

(6) L. P. Vinogradova, G. A. Kogan, and S. I. Zav'yalov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1061 (1964).

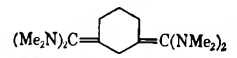
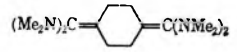
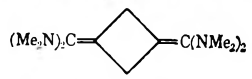
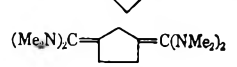
(7) C. S. Foote and J. Wei-Ping Lin, *Tetrahedron Lett.*, No. 29, 3267 (1968).

(8) M. M. Baizer, *J. Electrochem. Soc.*, **111** (2), 215 (1964).

(9) An esr study and an electrochemical study will be reported elsewhere: J. Fritsch, H. Weingarten, and J. D. Wilson, in press.

TABLE I

PHYSICAL CONSTANTS AND ELEMENTAL ANALYSES OF DIENETETRAMINES

Compd no.	Compd[a]	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Nmr, τ	Mp or bp, °C (mm)
12	$CH_2[CH{=}C(NMe_2)_2]_2$	52	65.1	11.6	23.3	64.9	11.5	23.6	(C_6H_6) 6.28 (t, 1, J = 7 Hz), 7.17 (t, 1, J = 7 Hz), 7.31 (s, 6), 7.61 (s, 6)	73 (0.1)
14	$+CH_2CH{=}C(NMe_2)_2]_2$	40	66.1	11.8		66.4	11.6		(C_6H_6) 6.25 (m, 1), 7.32 (s, 6), 7.58 (s, 6), 7.70 (m, 2)	85 (0.1)
15	$CH_2[CH_2CH{=}C(NMe_2)_2]_2$	74					...[b]		(C_6H_6) 6.30 (t, 1) 7,35 (s, 6), 7.61 (s, 6), 7.89 (m, 2), 8.44 (m, 1)	87 (0.1)
17		61	68.5	11.5	20.0	68.4	11.4	19.6	(CD_3CN) 7.34 (s, 1), 7.42 (s, 6), 7.44 (s, 6), 7.90 (m, 2), 8.45 (m, 1)	100 (0.15)
19		65	68.5	11.5	20.0	68.6	11.8	19.7	(C_6H_6) 7.38 (s, 3), 7.69 (s, 1)	83–85
21		73	66.6	11.2		66.9	10.9		(CD_3CN) 6.47 (s, 1), 7.46 (s, 1)	100 (0.2)
22		68					...[b]		(CD_3CN) 7.13 (m, 1), 7.42 (s, 12), 7.75 (m, 2)	98 (0.15)

[a] See ref 10. [b] These compounds are very atmosphere sensitive and in some cases we were not able to obtain satisfactory elemental analyses.

be a one-electron process, we have not been able to determine if the radical cation is dimerized to any extent. If the dimer exists, it must be in dynamic equilibrium with the radical cation.

The result of silver-ion oxidation of 2-methylpropenylidenebisdimethylamine [$(CH_3)_2C{=}C(NMe_2)_2$, **3**], although varying from the oxidation of **1**, is consistent with the formation of a radical cation intermediate. The only observable reaction is disproportionation, yielding an equal mixture of 1,1-bis(dimethylamino)-isobutylium nitrate [$(CH_3)_2\overset{+}{C}HC(NMe_2)_2NO_3^-$, **4**] and 1,1-bis(dimethylamino)methylallylium nitrate [$CH_2{=}C(CH_3)\overset{+}{C}(NMe_2)_2NO_3^-$, **5**].

Vinylidenebisdialkylamine (**6**), the parent enediamine of the series, yields yet a different result on oxidation. Dimerization takes place and the ultimate product

$$2CH_2{=}C(NMe_2)_2 + 2Ag^+$$
6

$$\downarrow$$

$$(Me_2N)_2\overset{+}{C}CH_2CH_2\overset{+}{C}(NMe_2)_2 + 2Ag$$
7

$$\downarrow 2\ (6)$$

$$(Me_2N)_2C{=}CHCH{=}C(NMe_2)_2 + 2CH_3\overset{+}{C}(NMe_2)_2$$
8

$$\downarrow 2Ag^+$$

$$(Me_2N)_2\overset{+}{C}CH{=}CH\overset{+}{C}(NMe_2)_2 + 2Ag$$
9

is 1,1,4,4-tetrakis(dimethylamino)-2-butene-1,4-diylium nitrate (**9**). The intermediate **7** is no doubt first formed and converted into 1,1,4,4-tetrakis(dimethylamino)butadiene (**8**) by reaction with additional **6**, and **8** is then rapidly oxidized to **9**. The compound **8** was prepared independently[10] and shown to be readily oxidized to **9**. A mixture of **8** and **9** in acetonitrile solvent is strongly esr active and the activity persists indefinitely.

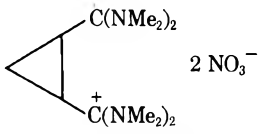
(10) H. Weingarten and W. A. White, *J. Org. Chem.*, **31**, 2874 (1966).

The results of the oxidation of propenylidenebisdimethylamine [$CH_3CH{=}C(NMe_2)_2$, **10**] further wakened our interest in the reaction for its possible synthetic utility as a carbon–carbon bond-forming process. When **10** is oxidized under the reaction conditions, the primary product is a *dl* and *meso* mixture of 1,1,4,4-tetrakis(dimethylamino)-2,3-dimethylbutane-1,4-diylium nitrate [$(Me_2N)_2\overset{+}{C}CH(CH_3)CH(CH_3)\overset{+}{C}(NMe_2)_2 \cdot 2NO_3^-$, **11**], corresponding to **7** above. Loss of protons to starting product **10** does not occur to any great extent, indicating that it may not be necessary to sacrifice half of a rather esoteric starting material in the process. The structural assignment of **11** was confirmed by independent synthesis.

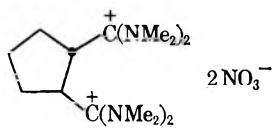
To explore the possible generality of the process we turned our attention to the interesting prospect of ring-forming reactions. A series of dienetetramines were prepared by methods already described[10] (see Table I) and subjected to oxidation. N,N,N′,N′,-N″,N″,N‴,N‴-Octamethyl-1,4-pentadiene-1,1,5,5-tetramine (**12**), on oxidation with silver nitrate, affords a high yield of a mixture of *cis*- and *trans*-cyclopropylenebis(dimethylaminomethylium) nitrate (**13**). The structural assignment was made by hydrolysis of **13** to the corresponding diamide and comparison with authentic diamide.[11] The *cis/trans* ratio in **13** is about 2:3, whereas the *cis/trans* ratio in the corresponding diamide is about 1:5. It is almost certain that **13** is isomerized in the hydrolysis media, since addition of trace amounts of **6**, a strong base, to an acetonitrile solution of **13** causes the nmr peaks attributed to the *cis* isomer to disappear while the *cis* diamide is stable to base. N,N,N′,N′,N″,N″,N‴,N‴-Octamethyl-1,5-hexadiene-1,1,6,6-tetramine (**14**), however, on oxidation gave only a complex mixture which included polymeric substances. Comparison of nmr spectra of this mixture with those of the expected authentic cyclobutane derivatives suggested that 1,2-cyclobutanes may be present, but in yields below 15%. No cyclobutane derivative was actually isolated.

(11) A. T. Blomquist and D. T. Longone, *J. Amer. Chem. Soc.*, **81**, 2012 (1959). The *cis* isomer was supplied by C. F. Hobbs, Monsanto Co., St. Louis, Mo.

As might be expected, five-membered rings are formed quite readily. N,N,N′,N′,N″,N″,N‴,N‴-Octamethyl-1,6-heptadiene-1,1,7,7-tetramine (**15**) is oxidized in high yield to 1,2-cyclopentylenebis(dimethylaminomethylium) nitrate (**16**). The structural assignment of **16** is based on its hydrolysis to diamide and comparison with authentic sample (only *trans* diamide is observed). The above three examples indicate that the normal order of ease of ring closure applies in this reaction.



13 (*cis* and *trans*)



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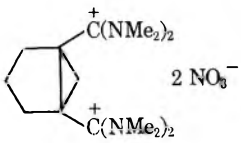

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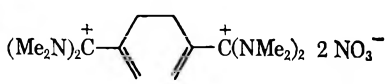

20

We next turned our attention to bicyclic synthesis. 1,3-Bis[bis(dimethylamino)methylene]cyclohexane (**17**) is smoothly and in high yield converted into bicyclo[3.1.0]cyclohexan-1,5-ylenebis(dimethylaminomethylium) nitrate (**18**). The structural assignment of **18** rests on its hydrolysis to diamide and comparison with authentic diamide.[12] The 1,4 isomer of **17**, 1,4-bis[bis(dimethylamino)methylene]cyclohexane (**19**), is converted not into the hoped for [2.2.0] system but into the expected open-chain 1,1,6,6-tetrakis(dimethylamino)-2,5-bis(methylene)hexane-1,6-diylium nitrate (**20**).

Attempts were also made to convert 1,3-bis[bis(dimethylamino)methylene]cyclobutane (**21**) and 1,3-bis[bis(dimethylamino)methylene]cyclopentane (**22**) into the corresponding bicyclo derivatives, but all attempts, even at low temperatures, failed to yield the desired products. It is possible, of course, that the bicyclic systems are formed but that the amidinium substituents considerably lower the barrier to the opening of the strained rings.

While no mechanistic studies, as such, have been carried out, a reasonable mechanistic model can be constructed based on the information at hand. If we accept the electrochemical evidence (esr, cyclic voltammetry, and coulometry) which suggests radical cations as the first intermediates, the chief remaining question is whether two radical cations dimerize or whether the radical cation reacts with starting enediamine. Two facts bear on this question: (1) we have not been able to induce free-radical polymerization of styrene or isoprene under conditions where the radical cation is believed to be generated (oxidation of **6**); (2) enediamine **6** is not incorporated into polyethylene formed by free-radical polymerization nor does it inhibit the ethylene polymerization. These experiments suggest the radical to be reasonably stable and a poor free-radical initiator, and the enediamine to be a poor radical sink. Therefore, we believe that the most plausible mechanistic model involves dimerization of two radical cations.

(12) H. Prinzbach, H. Hagemann, J. H. Hartenstein, and R. Kitzing, *Chem. Ber.*, **98**, 2201 (1965).

Experimental Section

Proton nmr spectra were obtained from a Varian Model A-60 spectrometer. Melting points and boiling points are uncorrected. All operations involving the ketene N,N-acetals were performed in an atmosphere of dry nitrogen.

Preparation of 9-[Bis(dimethylamino)methylene]fluorene Radical Cation Hexafluorophosphate (2).—To a solution of 0.250 g (1.47 mmol) of $AgNO_3$ in 5 ml of acetonitrile is added a solution of 0.370 g (1.40 mmol) **1** in 5 ml of acetonitrile. The reaction mixture turns deep blue immediately and a near quantitative precipitate of metallic silver appears. The solution is filtered and the filtrate is added to a 25-ml aqueous solution of $NaPF_6$ (excess). A dark precipitate of **2** is formed, collected, and dried: wt 0.43 g (75%). The precipitate is recrystallized from acetonitrile–methanol, yielding copper-colored crystals.

Anal. Calcd for $C_{18}H_{20}N_2PF_6$: C, 52.8; H, 4.9; N, 6.9. Found: C, 52.6; H, 4.9; N, 6.6.

Preparation of 1,1-Bis(dimethylamino)-2-methylallylium Tetraphenylborate (5a).[13]—To a solution of 2.4 g (0.014 mol) of $AgNO_3$ in 25 ml of acetonitrile is slowly added a solution of 2.0 g (0.0156 mol) of **3** also in 25 ml of acetonitrile. The reaction is exothermic and a black precipitate appears immediately. The solution above the precipitate is clear and colorless. The reaction mixture is filtered and an excess of ether is added, precipitating the nitrate-salt mixture. Solvent is removed from the solid, 2.5 g (90%), which is then dissolved in 20 ml of water. Sodium chloride solution is added to remove excess silver ion, the resulting mixture is filtered, and 0.5 equiv of KOH solution is slowly added with constant nmr monitoring. The resultant solution is added to a saturated solution of $NaB(C_6H_5)_4$ and a precipitate of **5a** is formed: yield 2.5 g (87%); nmr (DMSO-d_6) τ 2.75–3.26 (m, 20), 4.30 (m, 1), 4.50 (m, 1), and 6.98 (s, 12), and 9.14 (m, 3). This salt is recrystallizable from acetonitrile–water.

Anal. Calcd for $C_{32}H_{37}N_2B$: C, 83.5; H, 8.1; N, 6.1. Found: C, 83.6; H, 7.9; N, 6.1.

Preparation of 1,1,4,4-Tetrakis(dimethylamino)-2-butene-1,4-diylium Hexafluorophosphate (9a). Method I.—To a solution of 3.5 g (0.0206 mol) of $AgNO_3$ in 20 ml of acetonitrile is added slowly a solution of 2.28 g (0.0200 mol) of **6** in 10 ml of acetonitrile. The reaction is exothermic and black precipitate forms immediately. The reaction mixture is filtered and added to an excess of dry ether. A second phase oils out and is separated from the solvent layer. The second phase is dissolved in methanol and treated with $NaPF_6$, yielding a precipitate of **9a**: yield 2 g (78%);[14] nmr (CD_3CN) τ 2.86 (s, 1) and 6.78 (s, 12). This compound is recrystallizable from acetonitrile–ether.

Anal. Calcd for $C_{12}H_{26}N_4P_2F_{12}$: C, 27.9; H, 5.1; N, 10.9. Found: C, 28.2; H, 5.2; N, 10.8.

Preparation of 1,1,4,4-Tetrakis(dimethylamino)-2-butene-1,4-diylium Hexafluorophosphate (9a). Method II.—To a solution of 0.073 g (0.32 mmol) of **8** in 1 ml of acetonitrile is added slowly a solution of 0.11 g (0.65 mmol) of $AgNO_3$ also in 1 ml of acetonitrile. An exothermic reaction takes place producing a black precipitate and an amber solution which becomes colorless when the addition of silver salt is complete. The reaction mixture is filtered and the filtrate is added to excess ether. A second phase is formed which is separated from the solvent and then dissolved in methanol to which is then added $NaPF_6$. The precipitate which is formed, 0.15 g (90%), is identical in every way with that obtained by method I.

Preparation of 1,1,4,4-Tetrakis(dimethylamino)-2,3-dimethylbutane-1,4-diylium Hexafluorophosphate (11a).—To a solution of 3.6 g (0.021 mol) of $AgNO_3$ in 30 ml of acetonitrile is added slowly a solution of 2.5 g (0.019 mol) of **10** in 20 ml of acetonitrile. An exothermic reaction takes place producing a black precipitate and a light amber solution. This solution is decanted from the silver precipitate into 100 ml of dry ether. The second phase which forms is separated, dried, and then dissolved in methanol. This methanol solution is added to a saturated solution of $NaPF_6$ also in methanol. The precipitate of **11a** which forms is dried and can be recrystallized from acetonitrile–methanol: yield 2.2 g (42%); nmr (CD_3CN) τ 6.35 (m, 1), 6.75 and 6.81 (s, 12), and 8.54 and 8.66 (m, 3) (*dl* and *meso* in a ratio of about 1:3, not assigned).

(13) The letter **a** following a bold-face numeral signifies an anion other than nitrate.

(14) The yield is based on using one-half of compound **6** as a proton scavenger.

Anal. Calcd for $C_{14}H_{32}N_4P_2F_{12}$: C, 30.8; H, 5.9; N, 10.3. Found: C, 30.9; H, 6.0; N, 10.3.

Preparation of Cyclopropylenebis(dimethylaminomethylium) Hexafluorophosphate (13a).—To a solution of 2.0 g (0.012 mol) of $AgNO_3$ in 10 ml of acetonitrile is added slowly a solution of 1.2 g (0.0050 mol) of **12** in 15 ml of acetonitrile (1 ml of benzene added to solubilize amine). An exothermic reaction follows. The filtrate is decanted from the silver precipitate and the solvent is removed. The residue is dissolved in water and the product is precipitated by the addition of $NaPF_6$ solution. The precipitate of *cis*- and *trans*-**13a** can be recrystallized from acetonitrile–chloroform without significant fractionation: yield 2.24 g (85%); nmr (CD_3CN) τ 6.78 and 6.80 (s, 6) (*cis*/*trans* ratio 2:3), and 7.17–8.25 (m, 1).

Anal. Calcd for $C_{13}H_{28}N_4P_2F_{12}$: C, 29.5; G, 5.3; N, 10.6. Found: C, 29.7; H, 5.3; N, 10.3.

Hydrolysis of the above salt in dilute KOH solution yields a mixture of amides (*cis*/*trans* ratio, 1:5) identical with the authentic N,N,N′,N′-tetramethylcyclopropanedicarboxamides.[11]

Preparation of 1,2-Cyclopentylenebis(dimethylaminomethylium) Hexafluorophosphate (16a).—To a solution of 4.0 g (0.024 mol) of $AgNO_3$ in 40 ml of acetonitrile is added slowly a solution of 2.68 g (0.010 mol) of **15** in 20 ml of acetonitrile. The reaction is exothermic and a black precipitate is deposited. The reaction mixture is filtered, the filtrate is evaporated, and the residue is dissolved in water. This aqueous solution is treated with $NaPF_6$ yielding a precipitate of **16a**, which can be recrystallized from acetonitrile–chloroform: yield 5.1 g (91%); nmr (CD_3CN) τ 5.95–6.50 (m, 1), 6.79 (s, 12), and 7.35–8.05 (m, 3).

Anal. Calcd for $C_{15}H_{32}N_4P_2F_{12}$: C, 32.3; H, 5.8; N, 10.0. Found: C, 32.1; H, 5.6; N, 9.8.

Hydrolysis of the above salt in dilute KOH solution yielded a diamide identical with authentic *trans*-N,N,N′,N′-tetramethylcyclopentane-1,2-dicarboxamide (mass spectrum and nmr spectrum identical).

Preparation of Bicyclo[3.1.0]cyclohexan-1,5-ylenebis(dimethylaminomethylium) Hexafluorophosphate (18a).—To a solution of 3.7 g (0.022 mol) of $AgNO_3$ in 50 ml of acetonitrile is added slowly a solution of 2.8 g (0.01 mol) of **17** in 30 ml of acetonitrile (plus 5 ml of benzene to solubilize the amine). An exothermic reaction occurs yielding a clear solution and a black precipitate. The reaction mixture is filtered and the filtrate is evaporated. The residue is dissolved in water and treated with $NaPF_6$, which precipitates **18a**. The salt can be recrystallized from acetonitrile–chloroform: yield 5.0 g (88%); nmr (CD_3CN) τ 6.74 (s, 3) and 7.25–8.06 (m, 1).

Anal. Calcd for $C_{16}H_{32}N_4P_2F_{12}$: C, 33.7; H, 5.7; N, 9.8. Found: C, 33.4; H, 5.5; N, 9.6.

Hydrolysis of the above salt in dilute KOH solution yielded a diamide having an nmr spectrum identical with that of authentic N,N,N′,N′-tetramethyl[3.1.0]bicyclohexane-1,5-dicarboxamide.[12]

Preparation of 1,1,6,6-Tetrakis(dimethylamino)-2,5-bis(methylene)hexane-1,6-diylium Hexafluorophosphate (20a).—To a solution of 0.40 g (2.3 mmol) of $AgNO_3$ in 5 ml of acetonitrile is added slowly a solution of 0.25 g (0.89 mmol) of **19** also in 5 ml of acetonitrile. An exothermic reaction takes place depositing a black precipitate. The supernatant liquid remains clear and colorless. The supernatant liquid is decanted and the solvent is removed. The residue is dissolved in methanol and treated with $NaPF_6$, producing a precipitate of **20a** which is recrystallizable from acetonitrile–methanol: yield 0.46 g (90%); nmr (CD_3CN) τ 4.10 (s, 1), 4.26 (s, 1), 6.85 (s, 12), and 7.56 (s, 2).

Anal. Calcd for $C_{16}H_{32}N_4P_2F_{12}$: C, 33.7; H, 5.7; N, 9.8. Found: C, 33.9; H, 5.55; N, 10.0.

Registry No.—**2**, 12408-23-0; **5a**, 23883-43-4; **9a**, 23846-95-9; *dl*-**11a**, 23846-96-0; *meso*-**11a**, 23890-42-8; **12**, 23853-17-0; *cis*-**13a**, 23942-64-5; *trans*-**13a**, 23942-65-6; **14**, 23853-19-2; **15**, 23853-18-1; **16a**, 23846-97-1; **17**, 23853-20-5; **18a**, 23890-43-9; **19**, 23853-97-6; **20a**, 23846-98-2; **21**, 23853-98-7; **22**, 23853-99-8.

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The Thermal Cleavage of Selected Aldehyde Hyrazonium Salts

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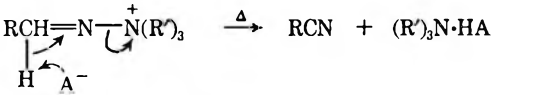
A series of aldehyde trimethylhydrazonium salts, $RCH{=}N{-}\overset{+}{N}(R')_3\ A^-$, has been pyrolyzed. This class of salts cleaved at temperatures of 240–250° to give low yields of the corresponding nitrile. Compounds prepared by replacing two of the three methyl groups with cyclic methylene substituents were found to undergo rapid cleavage at 240° to afford high yields of the desired nitrile.

A survey of the literature revealed several reports that aldehyde trimethylhydrazonium salts undergo a β elimination in alkaline solution to give good yields (51–93%) of the corresponding nitrile.[2-4] However, no study of the thermal decomposition of this class of compounds has been reported.

An interest in pyrolyzable precursors to nitriles prompted us to prepare and thermally cleave a series of aldehyde hydrazonium salts. It was proposed that a thermally induced β elimination might afford high yields of the desired nitrile and ammonium salt. It was felt that changing the basicity of the anion, A^-, as well as placing electron-withdrawing or -releasing groups on the aldehyde substituent (aromatic series), should effect the yield of nitrile. However, this approach was found to have less influence on the yield



of nitrile than did partial replacement of the methyl groups with bulkier substituents.

Discussion and Results

As an extension of our previously reported work,[5] a series of 38 trimethyl quaternary hydrazonium salts

(1) (a) To whom all correspondence should be addressed: Amoco Chemicals Corporation, Whiting, Ind. 46394. (b) Portions of this work were done by E. L. Anderson in partial fulfillment of the Ph.D. requirements of The American University.

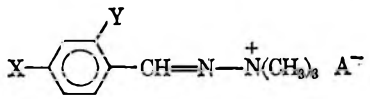
(2) R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27**, 4372 (1962).

(3) B. V. Zoffee and N. L. Zelevinia, *Zh. Org. Chem.*, **4**, 1558 (1969).

(4) K. N. Zelevin and B. V. Zoffee, *Vestn. Leningrad Univ., Fiz., Khim.*, **23**, 159 (1968).

(5) P. Foley, E. Anderson, and F. Dewey, *J. Chem. Eng. Data*, **14**, 272 (1969).

(1–3) was cleaved at temperatures between 240 and 250° for 2 or 10 min in a small pyrolysis apparatus. At



1

X	Y	A⁻
OCH_3	H	I^-, Ots^-,[6] BF_4^-, Cl^-, $SnCl_6^{-2}$
H	H	
NO_2	H	
Cl	Cl	

$CH_2[CH_2CH{=}N{-}\overset{+}{N}(CH_3)]_2\ A^-$

2

$A^- = I^-, Br^-, Cl^-, SnCl_6^{-2}, Ots^-, ClO_4^-, BF_4^-, PF_6^-, AsF_6^-, NO_3^-$

$NC(CH_2)_2C(CH_3)_2CH{=}N{-}\overset{+}{N}(CH_3)_3\ A^-$

3

$A^- = I^-, Cl^-, SnCl_6^{-2}, Ots^-, ClO_4^-, BF_4^-, PF_6^-, NO_3^-$

best, yields of less than 20% nitriles **4a** and **4b** were realized, with the formation of much heavy black tar. For aromatic nitriles **4a** the most product was obtained at pyrolysis times of 10 min; less time left much unchanged salt; longer times gave lower yields and more tar. For aliphatic nitriles **4b** a time of 2 min proved best. In addition to the desired nitriles **4a** and **4b** and the corresponding ammonium salt **5**, a side product from the reaction, hydrazones **6a** and

$$\mathbf{1, 2, 3} \xrightarrow{\Delta} \underset{\mathbf{4a, 4b}}{RCN} + \underset{\mathbf{5}}{(CH_3)_3N\cdot HA} + \underset{\mathbf{6a, 6b}}{RCH{=}N{-}N(CH_3)_2}$$

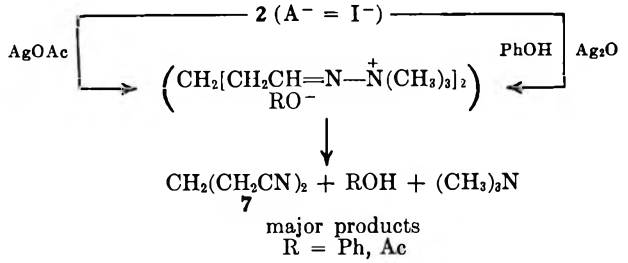
R = aromatic
R = aliphatic

6b (2–15%) were identified in all instances except those involving the perchlorate and nitrate salts of **2** and **3**, indicating loss of a methyl group during pyrolysis. Formation of hydrazones has been observed in the alkaline cleavage of trimethylhydrazonium salts and a mechanism involving nucleophilic attack by base on a methyl group has been proposed.[3,4]

Salts **1**, **2**, and **3** decomposed slowly below 200°, but the necessity for rapid reaction led to the use of 240–250° for pyrolysis. The salts darkened slightly above their melting points, then decomposed exothermically to give the desired products and much tar. The perchlorate and nitrate salts of **2** and **3** detonated at 240° to give fine black powders that were essentially inorganic. Nitriles **4b** and hydrazones **6b** were not detected (ir).

Cleavage of the iodide salts of **1**, **2**, and **3** led to the formation of an unexpected product. Tetramethylammonium iodide was isolated (45–47%) from each residue and its structure was authenticated by ir spectrum, melting point, and elemental analysis. In addition, the corresponding nitriles **4a** and **4b** and hydrazones **6a** and **6b**, in yields of 20 and 4%, respectively, were also found in the residues. After the removal of tetramethylammonium iodide and the corresponding **4a** and **4b** and **6a** and **6b**, the remaining material (tar) from each pyrolysis was subjected to ir analysis. Although the spectra were nondescript, absorptions at 2760 and 1640 cm^{-1} were assigned to trimethylammonium iodide (**5**, $A^- = I^-$). Attempts to identify other products in the residues were not made. The tetramethylammonium iodide is probably formed by the attack of trimethylamine on the iodide salts **1**, **2**, and **3**, the trimethylamine arising from pyrolyzed trimethylammonium iodide (**5**, $A^- = I^-$). Ir analysis of the residues obtained by heating equal molar amounts of hydrazone **6a** and **6b**, and trimethylammonium iodide (**5**, $A^- = I^-$) at 250° for 2 min (**6b**) and 10 min (**6a**) revealed spectra which were identical in every respect with those obtained from the individual pyrolysis residues.

Altering the basicity of the anion, A^-, did not produce a significant increase or decrease in the yields of nitriles **4a** and **4b**. A change of less than 5% was



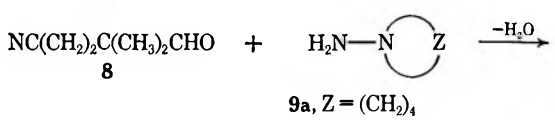
observed. Support for the mechanism of base-induced decomposition by the anion was realized by attempted preparation of the more basic acetate and phenoxide salts of **2**. Both compounds were found to eliminate *in situ* to glutaronitrile (**7**).[5] Hydrazones **6b** were not found in the reaction residues.

Only a small enhancement of the yield of desired nitrile **4a** from the pyrolysis of **1** (X = NO_2; Y = H) was observed, *i.e.*, a slight increase (<5%) in the yield of *p*-nitrobenzonitrile was noted. Likewise, a slight decrease (<5%) in the yield of anisonitrile was found when compounds of **1** (X = OCH_3; Y = H) were decomposed.

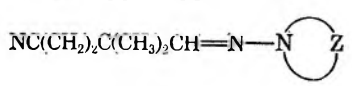
In summary, the aldehyde (R) or anion portions of the trimethyl salts **1**, **2**, and **3** had little effect on the yield of the desired nitrile. The cause of the low yields of nitrile was recognized as the lability of the quaternary methyl groups to nucleophilic attack.

For these reasons we concentrated our efforts on replacing the methyl groups with more sterically hindered alkyl groups to prevent dealkylation by nucleophilic attack. Likewise, we concentrated our efforts on two salts, the iodide and fluoroborate of a single aldehyde, 4-cyano-2,2-dimethylbutyraldehyde (**8**). Aldehyde **8** was chosen because of its commercial availability and because of an interest in the aliphatic dinitrile expected from the pyrolysis of its hydrazonium salts.

Aldehyde **8** was condensed with several cyclic hydrazines **9**. Formation of hydrazones **10** was in each



9a, Z = $(CH_2)_4$
b, Z = $(CH_2)_5$
c, Z = $(CH_2)_6$
d, Z = $(CH_2)_2O(CH_2)_2$

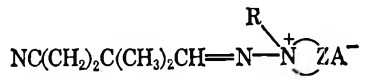


10a–d

(6) Ots, *p*-toluenesulfonate.

TABLE I

PREPARATION AND PROPERTIES OF HYDRAZONIUM SALTS



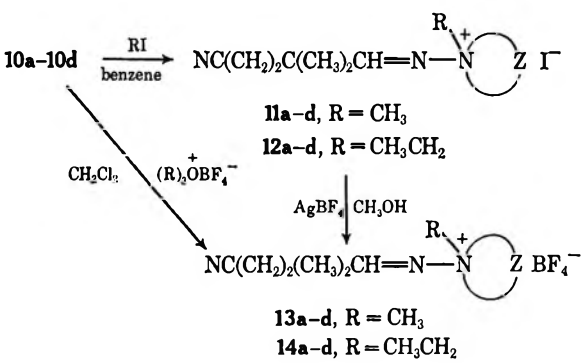
Compd	Z	R	A⁻	Yield, %	Mp, °C	S[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11a	$(CH_2)_4$	CH_3	I	90	70–75	P	$C_{12}H_{22}N_3I$	42.99	6.62	12.53	42.78	6.26	12.50
11b	$(CH_2)_5$	CH_3	I	99	114–116	P	$C_{13}H_{24}N_3I$	44.70	6.93	12.03	44.63	6.98	12.12
11c	$(CH_2)_6$	CH_3	I	76	149–150	P	$C_{14}H_{26}N_3I$	46.28	7.21	11.57	45.96	7.01	11.73
11d	$(CH_2)_2O(CH_2)_2$	CH_3	I	75	114–116	P	$C_{12}H_{22}N_3OI$	41.03	6.31	11.96	40.74	6.44	11.71
12a	$(CH_2)_4$	CH_3CH_2	I	83	84–86	P	$C_{13}H_{24}N_3I$	44.70	6.93	12.03	44.72	7.07	12.33
12b	$(CH_2)_5$	CH_3CH_2	I	80	119–120	E	$C_{14}H_{26}N_3I$	46.28	7.21	11.57	46.20	7.21	11.76
12c	$(CH_2)_6$	CH_3CH_2	I	70	136–138	E	$C_{15}H_{28}N_3I$	57.75	7.48	11.14	47.77	7.48	11.47
12d	$(CH_2)_2O(CH_2)_2$	CH_3CH_2	I	79	135–137	E	$C_{13}H_{24}N_3OI$	42.74	6.62	11.50	42.77	6.67	11.66
13b	$(CH_2)_5$	CH_3	BF_4	79 (1)[b] 89 (2)	70–72	E	$C_{13}H_{24}N_3BF_4$	50.50	7.82	13.59	50.73	7.71	13.70
13c	$(CH_2)_6$	CH_3	BF_4	75 (1) 87 (2)	70–71	P	$C_{14}H_{26}N_3BF_4$	52.03	8.11	13.00	52.00	7.84	13.08
13d	$(CH_2)_2O(CH_2)_2$	CH_3	BF_4	52 (1) 92 (2)	71–72	E	$C_{12}H_{22}N_3OBF_4$	46.32	7.13	13.51	46.34	7.15	13.49
14b	$(CH_2)_5$	CH_3CH_2	BF_4	87 (1) 91 (2)	78–79	M	$C_{14}H_{26}N_3BF_4$	52.03	8.11	13.00	52.32	8.33	12.71
14c	$(CH_2)_6$	CH_3CH_2	BF_4	80 (1) 87 (2)	91–93	E	$C_{15}H_{28}N_3BF_4$	53.42	8.37	12.46	53.68	8.21	12.27
14d	$(CH_2)_2O(CH_2)_2$	CH_3CH_2	BF_4	80 (1) 83 (2)	110–112	M	$C_{13}H_{24}N_3OBF_4$	48.02	7.44	47.91	7.58	7.58	12.72

[a] S, recrystallization solvent; P, isopropyl alcohol; E, ethanol; M, methanol. [b] Numbers in parentheses refer to the method of preparation.

case quantitative. The methyl and ethyl quaternary salts **11** and **12** were prepared by treating hydrazones **10** with methyl and ethyl iodide respectively. Yields of **11** were 75% or better while those of the ethyl salts **12** were slightly lower (Table I).

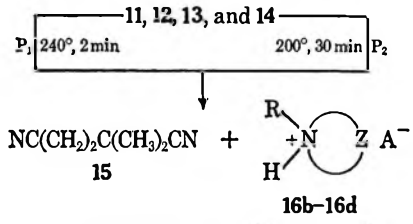
Fluoroborate compounds **13** and **14** were prepared to compare the yields of nitrile from their cleavage with those obtained from the pyrolyses of **11** and **12**. Both salts **13** and **14** were prepared by treating **11** and **12** with a methanol solution of silver fluoroborate. Salts obtained by this method were slightly colored (gray) and were difficult to purify. Trimethyl and triethyloxonium fluoroborate[7] were found to react rapidly and smoothly with hydrazones **10** and gave excellent yields of the fluoroborate salts **13** and **14** (Scheme

SCHEME I



I). Salts **13a** and **14a** were isolated as oils and were of no further interest in our work.

The series of iodide (**11** and **12**) and fluoroborate (**13** and **14**) hydrazonium salts reported in Table I were cleaved by two methods: P_1, rapid cleavage in a sealed tube at 240° for 2 min; P_2, slow pyrolysis at 200° for 30 min in an open system. Although excellent yields of 2,2-dimethylglutaronitrile (**15**) were found using rapid pyrolysis conditions (P_1), consistently higher yields of **15** were obtained when the salts were decomposed at 200° for 30 min (P_2). With iodides **11** and **12**, tar formation was negligible and higher yields of nitrile **15** were found than with fluoroborates **13** and **14**. The yields of hydrazones **10** using method



P_1 were 5% and only trace amounts were detected employing method P_2 (Table II).

TABLE II

YIELD OF PRODUCTS FROM PYROLYSIS OF QUATERNARY SALTS

Compd	% nitrile 15 P_1[a]	% nitrile 15 P_2	% hydrazones 10a-d P_1	% hydrazones 10a-d P_2
11a	90	90	2	T[b]
11b	73	80	2	T
11c	55	67	4	T
11d	95	95	T	T
12a	49	62	4	T
12b	80	91	T	T
12c	47	52	5	T
12d	78	87	T	T
13b	68	83	1	T
13c	55	78	5	T
13d	41	74	1	T
14b	19	82	5	T
14c	19	71	4	T
14d	47	76	2	T

[a] P_1 and P_2 refer to the method of pyrolysis. [b] T, trace.

(7) H. Meerein, *Org. Syn.*, **46**, 113, 120 (1900).

Benzene was used to extract both **15** and **10** from the residues and both compounds were identified by vpc analysis. An analytical sample of **15** for comparison purposes was independently prepared in 68% yield by the alkaline decomposition of **3** ($A^- = I^-$).

Although the benzene-insoluble residues were not of special interest, each was subjected to ir analysis. Peaks that could be attributed to $-C\equiv N$ (2240–2260 cm^{-1}) and $-C=N-$ (1620–1640 cm^{-1}) absorptions were not observed, evidencing complete extraction of nitrile **15** and hydrazones **10**. In fact, in the ir spectra of these residues no significant bands appeared which could not be assigned to the ammonium salt **16b–16d** ($-HN^+$, 2760–2763 cm^{-1}; BF_4^-, 1000–1100 cm^{-1}).[8]

Experimental Section[9]

Pyrolysis of Trimethylhydrazonium Salts (1, 2, and 3).—Samples (250 mg) of each salt were placed in a small Hickman-type microdistillation flask[10] equipped with two condenser alembics and lowered into a Wood's metal bath preheated to 240–250°. Aromatic salts **1** were pyrolyzed for 10 min and the aliphatic salts **2** and **3** for 2 min. In general, all salts cleaved with an exothermic reaction after 45 sec, except the perchlorate and nitrate salts of **2** and **3** which exploded after 30 sec.[11] The residues were extracted with benzene and the extracts were concentrated yielding anisonitrile, *p*-nitrobenzonitrile, and 2,4-dichlorobenzonitrile; each was identified by ir and melting point. The benzene extracts containing benzonitrile, glutaronitrile (**7**), and nitrile **15** were analyzed by vpc; the compounds were identified by mixed injections with authentic samples. Yields of all nitriles were less than 20%. The corresponding hydrazones **6a** and **6b** in the benzene extracts were identified by vpc. Yields of **6a** and **6b** were 2–15%. Analysis (ir) of the benzene-insoluble residues revealed NH^+ absorption at 2700–2765 cm^{-1}.

The residues from the cleavage of the iodide salts were washed from the pyrolysis flask with acetone and filtered. Trituration of the solid with hot methanol gave pure tetramethylammonium iodide, yield 63–97 mg (45–47%), darkened at 230°, mp >300° (lit.[12] mp >230° dec). Elemental analysis and ir further substantiated its structure. The acetone extracts were evaporated to give black residues. The residues were extracted with benzene. Nitriles **4a** and **4b** (20%) and hydrazones **6a** and **6b** were identified in the extracts by vpc analysis. Analysis of the benzene-insoluble materials by ir revealed NH^+ absorption at 2763–2765 cm^{-1}.

Reaction of Hydrazones 5a and 5b with Trimethylammonium Iodide (**5**, $A^- = I^-$).—Trimethylammonium iodide (**5**, $A^- = I^-$), 8×10^{-4} mol, was heated at 250° with 8×10^{-4} mol of hydrazones **4a** (10 min), and with 8×10^{-4} mol of **4b** (2 min). A comparison of the ir spectra of the residues with those obtained from the pyrolysis of salts **1**, **2**, and **3** revealed negligible differences in the occurrance of absorptions.

Preparation of Hydrazones 10.—4-Cyano-2,2-dimethylbutyraldehyde (**8**, 0.1 mol) and the appropriate hydrazine **9** (0.1 mol) were heated at reflux in 150 ml of benzene under a Dean–Stark trap until the theortical amount of water was collected (4–6 hr). The benzene solution was dried ($CaCO_3$), filtered, and concentrated, giving the hydrazones **10** as oils in quantitative yield.[13]

Preparation of Iodide Salts 11 and 12.—Hydrazones **10** (0.05 mol) in 75 ml of benzene and methyl or ethyl iodide (0.05 mol) were heated at reflux for 4 hr. The methyl salts **11** separated after 10 min. Precipitation of the ethyl salts **12** occurred after 1 hr. The salts were recrystallized from alcohol and characterized (Table I): ir (Nujol) $-C\equiv N$ (2250) and $-C=N-$ (1635–1640 cm^{-1}).

Preparation of Trimethyl and Triethyloxonium Fluoroborate.—Preparation of these compounds was conducted according to published directions.[7] Yields were 85–90%. Both compounds were stored under ether at −20°.

Preparation of Fluoroborate Salts 13 and 14. Method 1.—Freshly recrystallized iodide salts **11** and **12** (0.02 mol) were dissolved in 50 ml of warm methanol and added to a solution of silver fluoroborate (0.02 mol) in 20 ml of methanol. The mixture was stirred for 1 hr, filtered, and concentrated giving a crystalline product. Repeated recrystallization from alcohol gave pure **13** and **14** (Table I): ir (Nujol) $-C\equiv N$ (2250), $-C=N-$ (1635–1640), and BF_4^- (1000–1100 cm^{-1}).

Method 2.—Hydrazones **10** (0.01 mol) in 25 ml of methylene chloride were added to trimethyl or triethyloxonium fluoroborate (0.01 mol) in 50 ml of methylene chloride during 1 hr. The solution was heated at reflux temperature for 1 hr and the solvent was evaporated. Recrystallization from alcohol gave pure **13** and **14**.

Preparation 2,2-Dimethylglutaronitrile (**15**).—The method of Smith and Walker[2] was utilized. Recrystallized 4-cyano-2,2-dimethylbutyraldehyde trimethylhydrazonium salt (**3**, $A^- = I^-$), 276 g (0.9 mol) was dissolved in 600 ml of absolute methanol and heated at reflux with 48.6 g (0.9 mol) of sodium methoxide until the odor of trimethylamine disappeared. Addition of water (500 ml) and extraction with benzene (700 ml) gave **15**: ir (neat) $-C\equiv N$ (2250 cm^{-1}).

Anal. Calcd for $C_7H_{10}N_2$: C, 68.88; H, 8.19; N, 22.95. Found: C, 68.70; H, 8.16; N, 22.68.

Pyrolysis of Hydrazonium Salts 11–14. Method P_1.—Each quaternary salt (0.013 mol) was placed in a 6-in. glass tube (1.25-in. i.d.) and sealed. The tube was lowered into a Wood's metal bath preheated to 240°. Each sample was pyrolyzed for 2 min. The tube was cooled and broken, and the residue was extracted with benzene. Analysis by vpc revealed nitrile **15** and hydrazones **10** (Table II). The benzene-insoluble materials, under analysis by ir, revealed prominent bands at 2760–2765 ($-NH^+$) and 1000–1100 cm^{-1} for **16** ($A^- = BF_4^-$).

Method P_2.—Each salt was placed in a Hickman-type microdistillation flask equipped with two condensation alembics, heated slowly to 200° in a sand bath, and kept at that temperature for 30 min. The residues were cooled, extracted with benzene, and analyzed for **15** and **10** as in method P_1.

Registry No.—**11a**, 23649-85-6; **11b**, 23649-86-7; **11c**, 23649-87-8; **11d**, 23649-88-9; **12a**, 23674-47-7; **12b**, 23645-66-1; **12c**, 23645-67-2; **12d**, 23645-68-3; **13b**, 23645-58-1; **13c**, 23645-59-2; **13d**, 23645-60-5; **14b**, 23645-61-6; **14c**, 23645-62-7; **14d**, 23645-63-8.

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecule," 2nd ed' John Wiley & Sons, Inc., New York, N. Y., 1963, p 260.

(9) Melting points were determined in open capillaries and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by the National Bureau of Standards, Gaithersburg, Md. Infrared spectra were determined in mineral oil on a Beckman IR-5 spectrophotometer. Gas chromatograms were recorded on a Varian Aerograph Model 1520c with a thermal conductivity detector using a stainless steel 6 ft × 1/8 in. column packed with 5% EGP, 80–100 mesh, DMCS treated, on Chromasorb W.

(10) K. C. D. Hickman, *Chem. Rev.*, **34**, 51 (1944).

(11) The residues were analyzed by ir and appeared to be inorganic. The nitriles **4b** and hydrazones **6b** were not found (vpc).

(12) E. Chablay, *Ann. Chim.*, **1**, 469 (1914).

(13) The pyrrolidine hydrazone **10**, Z = $(CH_2)_4$, was prepared by treating N-aminopyrrolidine hydrochloride with triethylamine followed by reaction with aldehyde **8**.

The Photocycloaddition of Carbostyril to Olefins. The Stereochemistry of the Adducts

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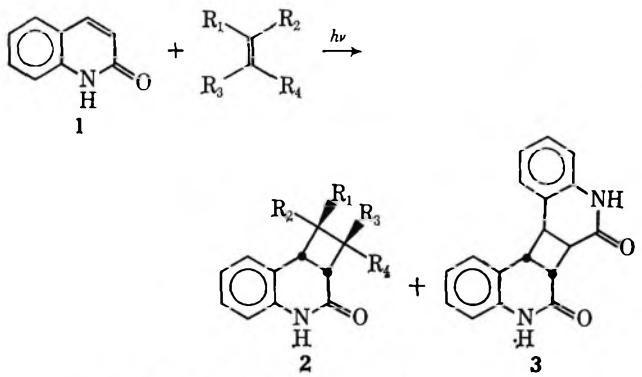
The photocycloaddition of carbostyril to olefins gives a series of dihydrocyclobuta[c]-2-quinolones in a regiospecific manner. The stereochemistry of these products indicates that the reaction proceeds to form selectively the head-to-tail adducts.

Cyclic enone photocycloaddition to olefins has been used extensively for the synthesis of cyclobutanes[2] and has provided the means for synthesis of cubane,[3a] atisine,[3b] bourbonenes,[4] caryophyllenes,[5] β-himachalene,[6] and a variety of other natural products[7] and extremely novel structures.[2] We have investigated the photocycloaddition of carbostyrils **1** (cyclenone heteroanalogs) to olefins because of its utility in synthesis of the unique tricyclic system **2**.

The cyclobutane derivatives of carbostyrils are readily synthesized photochemically without the aid of sensitizers in good to excellent yields. Carbostyril dimerization usually accompanies the cycloaddition reaction, and the yield of dimer is dependent on concentration, solvent, and olefin. A series of adducts was prepared from carbostyrils and olefins and is described in Scheme I. In general, a ratio of 10 equiv of olefin to 1 equiv of carbostyril was used at various concentrations in ethanol or N,N′-dimethylacetamide. Reactions were followed by tlc and usually run to completion. The results are summarized in Table I.

SCHEME I



1 → **2** + **3**

a, $R_1 = R_2 = R_3 = R_4 = CH_3$
b, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
c, $R_1 = R_2 = CH_2CH_3$; $R_3 = R_4 = H$
d, $R_1 = R_2 = OCH_3$; $R_3 = R_4 = H$
e, $R_1 = OCH_3$; $R_2 = R_3 = R_4 = H$
f, $R_1 = CN$; $R_2 = R_3 = R_4 = H$
g, $R_1 = OCOCH_3$; $R_2 = R_3 = R_4 = H$
h, $R_1 = O(CH_2)_3CH_3$; $R_2 = R_3 = R_4 = H$
i, $R_1 = R_2 = R_3 = R_4 = Cl$
j, $R_1 = R_2 = Ph$; $R_3 = R_4 = H$
k, $R_1 = R_3 = -CH_{2-3}$; $R_2 = R_4 = H$
l, $R_1 = R_3 = -CH_{2-6}$; $R_2 = R_4 = H$

TABLE I

Compd	Concn of 1[a]	Solvent	Irradn time,[b] hr	Yield of adduct, %	Yield of dimer 3, %
2a	69	Ethanol	20	90	9.4
2b	69	Ethanol	72	57	40
2c	41	Ethanol	72	50	50
2d	0.69	Dimethyl-acetamide	24	100	0
2e	69	Ethanol	144	65	35
2f	50	Ethanol	96	63	37
2g	69	Ethanol	72	8	22
2h	69	Ethanol	48	79	20
2i	50	Dimethyl-acetamide	96	71	5
2j	6.9	Ethanol	192	20	20
2k	69	Ethanol	72	54	46
2l	69	Ethanol	144	49	43

[a] Concentration of **1** × 10^3 *M*. [b] Irradiation time for a total volume of 700 ml of solvent irradiated in the Rayonet apparatus with 16 black-light lamps.

We have already presented some evidence to support the assigned structures **2** in a preliminary communication.[8] In addition, Loev, *et al.*,[9] have described similar products from 6-trifluoromethyl-N-methylcarbostyril and olefins, and Buchardt[10] has observed results related to ours. The photochemical dimerization of **1**,[11] N-methylcarbostyril,[11] and 6-trifluoromethyl-N-methylcarbostyril[9] has been described, and the stereochemistry of the dimers has been elegantly elucidated.[11]

Besides the elemental analyses, which are summarized in Table II, our evidence for the cycloadducts is based mainly on spectral data. The ir lactam carbonyl band of **2a** is in reasonable agreement with that of 3,4-dihydrocarbostyril (1671 and 1675 cm^{-1},[12] respectively, Nujol mull). The uv maximum of **2a** [λ_{max}^{EtOH} 259 mμ (ε 8600)] is shifted to lower frequency from that of 3,4-dihydrocarbostyril [λ_{max}^{EtOH} 250 mμ (ε 12,000)].[12] The ir and uv spectra of the other cycloadducts (**2**) also exhibit these shifts to lower frequency, and similar data were observed by Buchardt for the dimers **3** [$\lambda_{max}^{dioxane}$ 259 mμ (log ε 4.23)].[11b]

The mass spectra of the adducts exhibit weak parent molecule ions; the major ion is consistently due to

(1) To whom correspondence should be addressed: Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Conn.

(2) P. E. Eaton, *Accounts Chem. Res.*, **1**, 50 (1968); P. de Mayo, J.-P. Pete, and M. Tchir, *Can. J. Chem.*, **46**, 2535 (1968), and references cited therein.

(3) (a) P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 962 (1964); (b) R. W. Guthrie, A. Phillip, F. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 2945 (1965).

(4) J. D. White and D. N. Gupta, *J. Amer. Chem. Soc.*, **88**, 5364 (1966).

(5) E. J. Corey, R. B. Mitra, and H. Uda, *ibid.*, **86**, 485 (1964).

(6) B. D. Challand, G. Kornis, G. L. Lange, and P. de Mayo, *Chem. Commun.*, 704 (1967).

(7) H. Hikino and P. de Mayo, *J. Amer. Chem. Soc.*, **86**, 3582 (1964), and references cited therein.

(8) G. R. Evanega and D. L. Fabiny, *Tetrahedron Lett.*, 2241 (1968).

(9) B. Loev, M. M. Goodman, and K. M. Snader, *ibid.*, 5401 (1968).

(10) O. Buchardt, personal communication.

(11) (a) O. Buchardt, *Acta Chem. Scand.*, **17**, 1461 (1963); (b) O. Buchardt, *ibid.*, **18**, 1389 (1964).

(12) P. T. Lansbury and N. R. Mancuso, *J. Amer. Chem. Soc.*, **88**, 1205 (1966).

TABLE II
ELEMENTAL ANALYSES OF CYCLOADDUCTS

Compd	Adduct formula	Carbon		Hydrogen		Nitrogen		Oxygen	
		Calcd, %	Found, %	Calcd, %	Found, %	Calcd, %	Found, %	Calcd, %	Found, %
2a	$C_{15}H_{19}NO$	78.56	78.39	8.35	8.39	6.11	6.13	6.98	7.08
2b	$C_{13}H_{15}NO$	77.58	77.60	7.51	7.55	6.96	7.27	7.95	8.17
2c	$C_{15}H_{19}NO$	78.56	78.53	8.35	8.35	6.11	6.07		
2d	$C_{13}H_{15}NO_3$	66.93	66.96	6.48	6.41	6.01	5.86	20.58	20.85
2e	$C_{12}H_{13}NO_2$	70.91	71.03	6.45	6.50	6.89	7.04	15.75	15.97
2f	$C_{12}H_{10}N_2O$	72.71	72.67	5.09	4.98	14.13	13.97		
2g	$C_{13}H_{13}NO_3$	67.52	67.53	5.67	5.62	6.06	6.03		
2h	$C_{15}H_{19}NO_2$	73.44	73.30	7.81	7.88	5.71	5.82	13.04	13.12
2i	$C_{11}H_7NOCl_4$[a]	42.48	42.60	2.27	2.20	4.50	4.59		
2j	$C_{24}H_{19}NO$	84.89	84.85	5.89	5.60	4.30	4.33		
2k	$C_{14}H_{15}NO$	78.84	78.89	7.09	7.12	6.57	6.33	7.50	7.51
2l	$C_{17}H_{21}NO$	79.96	80.30	8.29	8.42	5.49	5.14		

[a] Calcd: Cl, 45.59. Found: Cl, 45.45.

carbostyril (*m/e* 145) from the loss of photocycloadded olefin.

The most compelling evidence for the assigned structure is given by the nmr spectra. For example, the spectrum of **2a** ($CDCl_3$, TMS) has four methyl singlets at δ 0.83, 1.13, 1.32, and 1.36, four aromatic hydrogens at δ 7.13 (m), and an AB pattern for the C-3 and C-6 cyclobutane hydrogens at δ 3.40 and 3.57 (J_{AB} = 10.3 Hz), respectively. The large coupling constant is consistent with *cis* vicinal hydrogens in a rigid cyclobutane ring, and would therefore indicate *cis* ring fusion.[13]

trans ring fusion of six- and four-membered rings has been observed in photochemical cycloadditions of cyclohexenone[14a] and 4,4-dimethylcyclohexenone.[14b] It was also observed in 6–4 and 5–4 fused-ring systems of cyclohexadiene and cyclopentadiene with dichloromaleic anhydride.[15] However, the coupling of an intermediate biradical leading to *trans* ring juncture is less probable in our system because of the steric constraints of the fused benzene ring and the amide function.

The stereochemical assignment of substituents on cyclobutane rings by nmr is untenable when it is based purely on the supposition that *cis* vicinal coupling constants will be larger than *trans*. In many cases $J_{cis} \cong J_{trans}$ owing to fast conformational averaging, and in other cases they are nearly equivalent owing to puckering in the molecule that significantly alters the vicinal dihedral angles from 0° (*cis*) and 120° (*trans*),[13] or to fast conformational averaging. A good example of this phenomenon is found in the nmr spectrum of anemonin, which has two J_{cis} values of 10.2 Hz, a J_{trans} value of 10.7 Hz, and a J_{trans} value of 2.2 Hz.[16] However, in cases of rigid, planar cyclobutanes, the *cis* vicinal coupling constants have been shown to be significantly larger than the *trans; e.g.*, cyclobutanone is reported to have a J_{cis} value of 10.02 Hz and a J_{trans} value of 6.35 Hz.[17]

Structure assignment on the basis of size of coupling constants has been used by others,[18] but in view of the above controversy over *cis* and *trans* couplings we attempted to further corroborate our *cis* assignment. In the photoaddition of 4,4-dimethylcyclohex-2-enone to dimethyl ketene acetal, Chapman, *et al.*,[19] found that both *cis* and *trans* ring-fusion products were obtained. They were able to convert the kinetically formed *trans* adduct into the thermodynamically more stable *cis* product with base.

By analogy, if **2a** had a *trans* ring juncture, treatment with base should give the *cis* ring-fused product. Compound **2a** was treated with 3.5 equiv of *n*-butyllithium and 1,4-diazabicyclo[2.2.2.]octane in tetrahydrofuran at 0°. After 2.5 hr half of the reaction was quenched with H_2O and half with D_2O. The reaction mixtures were separated by column chromatography, and the fractions corresponding to **2a** were analyzed by nmr. The nmr of the adduct from the D_2O treatment indicated 100% D incorporation (the cyclobutane hydrogen AB pattern of **2a** was replaced by a single, somewhat broad, resonance line at δ 3.58 corresponding to the C-6 hydrogen). The nmr spectrum of the adduct from the H_2O treatment was identical with that of the starting material **2a**. This evidence strongly supports the supposition of *cis* ring fusion for **2a** and presumably for other adducts **2**.

In the compounds described below, which are specific examples of adducts obtained from unique types of olefins, we will discuss the nmr spectra in detail. This is necessary because of the aforementioned controversy over nmr data of cyclobutane rings, and because there is only limited analysis of these systems reported to date.[8,9,11,18]

The structure of adducts from unsymmetrical 1,1-disubstituted olefins is not immediately predictable, since both head-to-head (**2m**, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$) and head-to-tail (**2b**, $R_3 = R_4 = H$; $R_1 = R_2 = CH_3$) adducts could be expected. In the pioneering work on photocycloaddition of cyclenones to unsymmetrical olefins, Corey, *et al.*,[14] observed a 3:1 preference for head-to-tail over head-to-head products from cyclohexenone and isobutylene. Thus it is quite reasonable to expect a mixture of isomers from the irradiation of carbostyrils with similar olefins. However, after careful analysis by vpc, tlc, and nmr, we were not able to detect the presence of more than one isomer from

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(14) (a) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (b) P. J. Nelson, D. Ostrem, J. D. Lassila, and O. L. Chapman, *J. Org. Chem.*, **34**, 811 (1969).

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(18) J. W. Hanifin and E. Cohen, *Tetrahedron Lett.*, 1419 (1966).

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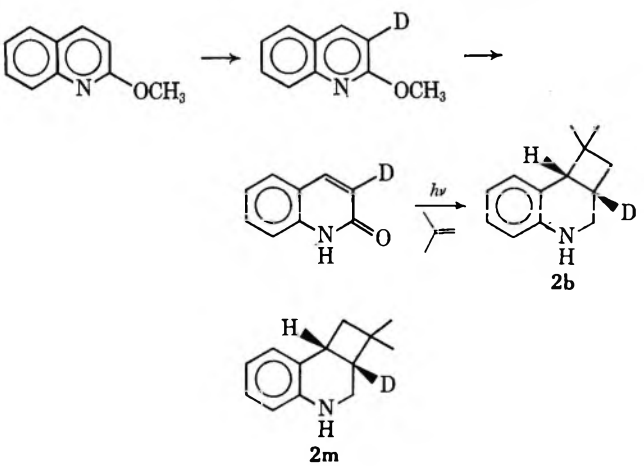
the photoaddition of any carbostyril to a 1,1-disubstituted olefin.

The 60-MHz nmr spectrum of the isobutylene carbostyril cycloadduct **2b** is quite complex; in CF_3CO_2D the methylene and methine cyclobutane hydrogens are broad multiplets at δ 2.38 (2 H) and 3.5 (2 H), respectively. The compound was analyzed on a 220-MHz instrument and a simple first-order spectrum in $CDCl_3$ (TMS) for the four-proton system was obtained; the specific chemical shifts and coupling constants are tabulated in Table III, on the basis of which we tentatively assigned structure **2b**.

TABLE III
220-MHz NMR DATA ($CDCl_3$) FOR 2b

		J, Hz		
H	δ, ppm	4-*exo*	4-*endo*	6
3	3.35	10.0	4.5	10.0
4-*exo*	2.49		−12.0	
4-*endo*	2.21			
6	3.50			

Further proof was obtained by preparation of C-3 deuterium-labeled carbostyril from 2-methoxyquinoline by treatment with *n*-butyllithium and D_2O followed by acid hydrolysis. The photocycloaddition of the 3-deuterocarbostyril to isobutylene gave the 3-deuterio-6-hydrocyclobuta[*c*]-2-quinolone. The nmr spectrum (CF_3CO_2D) of the cyclobutane hydrogens was a simple



2b

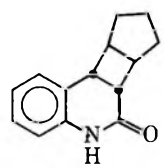
2m

ABM pattern: a singlet at δ 3.68 (1 H) and a quartet at δ 2.33 and 2.68 (2 H, J_{AB} = 12.1 Hz). Double-resonance nmr experiments indicated that cross-ring coupling was present: $|J_{6,4\text{-}exo}|$ = 0.84 Hz and $|J_{6,4\text{-}endo}|$ = 0.68 Hz. These values are of opposite sign, but it was not possible to determine the absolute value of each. In addition, the low-field methylene proton is weakly coupled (0.5 Hz > J > 0.0 Hz) with the high-field methyl group. This spectrum is compatible only with the head-to-tail adduct **2b**; the head-to-head isomer **2m** would be expected to have larger coupling constants for the vicinal hydrogens (J_{AM}, $J_{BM} \cong$ 6–10 Hz), producing a more complex ABM pattern than that observed (J_{AM}, J_{BM} <1 Hz).

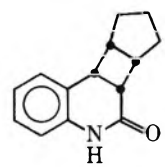
In addition it was possible to exchange the C-3 hydrogen of certain adducts for deuterium by treating them with butyllithium–DABCO and quenching with D_2O as described above. The nmr of the product from this treatment of **2b** after purification by chromatography was identical with that obtained from the photocycloaddition reaction of 3-deuteriocarbostyril and isobutylene. By this deuterium-labeling method we were able to simplify the four-proton nmr spectra of other 1,1-disubstituted adducts to a three-spin system and thereby confirm the head-to-tail photochemical addition. Furthermore, this method of incorporation of deuterium offers a more convenient alternative to the aforementioned synthesis of 3-deuteriocarbostyril.

By first approximation, cycloalkenes should give *syn* and *anti* fused-ring products on reaction with carbostyril. However, in view of carbostyril's dimerization to a single head-to-head *anti* ring-fused product, we expected to observe a single product from cyclopentene or cyclooctene addition.

The product **2k** from irradiation of **1** and cyclopentene appeared to be one product from vpc, tlc, and nmr data. The A-60 nmr spectrum was quite complex and the stereochemistry of the product was not known. However, the 220-MHz nmr spectrum ($CDCl_3$) not only helped elucidate the structure but also indicated the presence of two isomers in the reaction mixture: the *anti* ring-fused adduct **2k** and the *syn* adduct **2k′** in a



2k



2k′

3:1 ratio. The 220-MHz nmr data are presented in Table IV.

TABLE IV
220-MHz NMR DATA ($CDCl_3$) FOR 2k AND 2k′

		J, Hz						J, Hz		
H	δ, ppm	4	8	9	5–7	H	δ, ppm	4	8	9
3	2.88	4.5		9.7	0	3	3.92	10.5		10.5
4	3.10		7		7.0	4	3.36		10.5	
8	2.72			4.5	7.0	8	3.3			10.5
9	3.21				0	9	4.00			
5/7	1.92									

The four cyclobutane hydrogens of **2k** were readily identifiable by first-order analysis: H-3 and H-9 formed a four line pattern—a doublet of doublets—with J values of 4.5 and 9.7 Hz; H-4 and H-8 gave a six-line pattern—two sets of triplets each—with J values of 4.5, 7.0, and 7.0 Hz.

The structure **2k′** was assigned on the basis of the low-field triplets of H-3 and H-9 with the large J values of 10.5 Hz. This is consistent with four *cis* hydrogens on a cyclobutane ring. The upfield proton H-4 (or H-8) was further split by *ca.* 7 Hz by the methylene hydrogens C-5 and C-7. Part of the H-8 (or H-4) resonance signal was masked by H-9 of **2k**, and a complete analysis is not possible.

In view of the data from cyclopentene addition, one could expect, with monosubstituted unsymmetrical olefins, not one head-to-tail adduct, but a mixture[20] of two isomers with *exo* and *endo* substituents. The photocycloaddition of carbostyril to vinyl methyl ether should produce epimers (*exo*- and *endo*-methoxy) and possibly isomers owing to direction of addition (4- or

(20) This is consistent with our vpc data for adducts with these olefins; however, the cyclopentene adduct gave one peak in the vpc.

5-methoxy from head-to-head or head-to-tail addition) and type of ring fusion (*cis* or *trans* at C-3 and C-6). Only *exo*-5- and *endo*-5-methoxy epimers with a *cis* fused-ring juncture were found. This might be expected in that vinyl methyl ether should react similarly to dimethyl ketene acetal and give the *cis* ring-fused, head-to-tail products. However, acrylonitrile could give either the 5- or 4-cyano mixture depending on the preferred reaction mechanism. A biradical intermediate would favor a 5-cyano mixture, while a dipole–dipole interaction mechanism favors the 4-cyano mixture.

The irradiation of **1** with vinyl methyl ether, followed by subsequent removal of dimer and chromatography, gave the mixture **2e** in 33% yield. The analysis of the 220-MHz nmr spectrum revealed a 56:44 mixture of the *exo*- to *endo*-5-methoxy adducts. After three recrystallizations from acetone, the pure *exo*-5-methoxy-3,6-dihydrocyclobuta[*c*]-2-quinolone was obtained in 4% yield. The main support for the proposed structure is the nmr data of the pure isomer presented in Table V.

TABLE V
220 MHz NMR DATA ($CDCl_3$) FOR *exo*-**2e**

		J, Hz			
H	δ, ppm	4-*endo*	4-*exo*	5-*endo*	6
3	3.26	3.0	10.0	1.5	10.0
4-*endo*	2.78		12.0	7.0	1.0
4-*exo*	2.54			7.0	
5-*endo*	4.04				7.0
6	3.64				

The five cyclobutane hydrogens are readily identifiable by their first-order patterns: H-6 is a doublet of doublets that is coupled to the *cis* vicinal H-3 by 10.0 Hz and to the *trans* vicinal H-5 by 7.0 Hz; H-3 is a triplet with one portion masked by the OCH_3 at 3.30 ppm and the other two resonances further split by 3.0 and 1.5 Hz; H-5 is a quartet with 7.0-Hz splitting and with secondary splitting of 1.5 Hz; H-4 *exo* is a triplet of doublets (the center lines of the quartet are split by 3.0 Hz); and H-4 *endo* is a somewhat complex 16-line pattern incorporating all of the observed J values.

The assignment of the head-to-tail structure is strongly supported by deuterium-exchange experiments and the nmr spectra. The assignment of the *exo* position for the methoxy group is consistent with the expectation that the major epimer of the reaction mixture should have this configuration. Further support can be obtained from the magnitude of the $^3J_{vic}$ for the H-3, H-4, and H-5 hydrogens. A thorough analysis[21] of this system supports the puckered form of the cyclobutane ring, allowing the methoxyl group to assume the equatorial position.

We have not been able to separate the isomers by chromatography and have had to rely on the nmr of the mixture to confirm the identity of the other isomer. There is considerable overlap between the resonance signals of the two isomers, and a complete analysis of the minor product (*endo*-5-methoxy) is not possible.

The irradiation of carbostyril and acrylonitrile gave a considerable amount of dimer (37%) and some adduct **2f** (42%). We have been able to isolate the lower R_f isomer (on silica gel tlc) by recrystallization from ethanol in 16% yield. Based on the 220-MHz spectrum, we have assigned the cyano group the 5-*endo* position (see Table VI).

TABLE VI
220-MHz NMR DATA (DMSO-d_6) FOR THE *endo*-5-CYANO ISOMER **2f**

		J, Hz			
H	δ, ppm	4-*exo*	4-*endo*	5-*exo*	6
3	3.38	9.0	6.5	1.0	9.0
4-*exo*	2.89		12.0	9.0	1.5
4-*endo*	2.38			6.5	1.0
5-*exo*	3.85				9.0
6	4.15				

Four of the five cyclobutane hydrogens are readily identifiable by their first-order patterns: H-5 *exo* is masked by protons in the solvent; H-6 is a broad triplet ($W_{1/2}$ = 4 Hz) at δ 4.15; H-3 is an imperfect quartet at δ 3.85 with secondary splitting; H-4 *exo* is also an imperfect quartet with secondary splitting; and H-4 *endo* is a doublet of triplets with some overlap to give a five-line pattern.

A more thorough discussion of the nmr of **2f** has been presented elsewhere.[21] The observed coupling constants for H-3, H-4, and H-5 are consistent with the assignment of the 5-cyano group to an equatorial position on a puckered cyclobutane ring.

Although we have not been able to isolate the other isomer, an analysis of the 220-MHz nmr spectrum of the reaction mixture indicates a 40:60 mixture of *exo*- to *endo*-5-cyano-3,6-dihydrocyclobuta[*c*]-2-quinolone. This 40:60 ratio of *exo* to *endo* epimers is inconsistent with what one would expect for a bulky substituent based on the vinyl methyl ether case.

Recently, it was reported[22] that the acetophenone-photosensitized cycloaddition of indene to acrylonitrile gave a 50:45 ratio of *exo*- to *endo*-7-cyano-2,3-benzobicyclo[3,2,0]hept-2-ene. Direct irradiation of either isomer gave a photostationary state composed of a 45:55 *exo*- to *endo*-7-cyano mixture. Equilibrium studies with *t*-butoxide found a 70:30 *exo*- to *endo*-cyano ratio at 25°. These variations in ratio, although small, discount the steric influence of the cyano group.

In view of these results, any interpretation of our data at this time would indicate our lack of understanding of the reaction mechanism, including the specific function of the substituent on the olefin. However, one comment can be made about the mechanism at this time. Since the 5-cyano and not the 4-cyano epimer mixture was obtained, the nature of the product would seem to be determined by "the more stable biradical intermediate" theory and not by a dipole–dipole interaction mechanism. Further information on the mechanism of photocycloaddition will be published at a later date.

Experimental Section

Infrared spectra were recorded on a Beckman IR-10 spectrophotometer. Ultraviolet spectra were taken on a Cary 14 recording spectrophotometer. In general, nmr spectra were obtained on a Varian Associates A-60 spectrometer. All 220-MHz nmr spectra were run by Varian Associates, Palo Alto, Calif.

(21) E. B. Whipple, Jr., and G. R. Evanega, *Org. Magnetic Resonance*, **2**, 1 (1970).

(22) J. J. McCullough and C. W. Huang, *Can. J. Chem.*, **47**, 757 (1969).

Column chromatography was done on 0.05–0.2-mm silica gel (E. Merck, Darmstadt) from Brinkmann Instruments, Westbury, N. Y. Analytical precoated tlc plates of silica gel F-254 with fluorescent indicator (E. Merck, Darmstadt) were obtained from Brinkmann Instruments. Unibars were from Analtech, Wilmington, Del.

Vpc work was done on a Hewlett–Packard (F & M Scientific) Research Chromatograph, Model 5750, using a 6 ft × 0.125 in. column of 10% silicone gum rubber (UC-W98) on Chromosorb G (80–100 mesh, AW-DMCS).

Photocycloadditions of Carbostyrils with Olefins.—In general a 0.03–0.18 *M* solution of the carbostyril and 10 equiv of olefin in a suitable solvent (N,N-dimethylacetamide or ethanol) was purged with nitrogen and irradiated through quartz in the Srinivasan–Griffin photochemical reactor of the Southern New England Ultraviolet Co. equipped with 3500-Å fluorescent lamps. The irradiation was followed by tlc [10% (v/v) 2-propanol in benzene] and continued until the starting material disappeared (20 hr–2 weeks). The ethanolic irradiation mixtures were filtered to remove the precipitated dimer, and the filtrate was concentrated to dryness on a rotary evaporator. In other solvents the solution was concentrated and the residue was triturated or extracted with ethanol to separate the dimer. The products were purified normally by recrystallization, evaporative distillation, or sublimation. In a few cases, as indicated in the text, the reaction mixtures were separated by column chromatography. All reaction mixtures when analyzed by vpc gave one peak with the retention expected for the adduct unless otherwise specified.

4,4,5,5-Tetramethyl-3,6-dihydrocyclobuta[*c*]-2-quinolone (2a).—Compound **1** (10.0 g) and tetramethylethylene (58 g) in a 700-ml ethanol solution gave 0.94 g of **3** and 14.3 g of **2a**: mp 197–198.5° (from acetone, 63% overall yield); ir (KBr) 1666 cm^{-1} (amide C=O); uv λ_{max}^{EtOH} 259 mμ (ε 8600); nmr ($CDCl_3$) δ 9.48 (brs, 1, NH), 6.98 (m, 4, ArH), 3.26 (q, 2, J_{AB} = 10.4 Hz, cyclobutane CHCH), and 1.30, 1.19, 1.05, and 0.78 ppm (4 s, 12, 4 CH_3).

5,5-Dimethyl-3,6-dihydrocyclobuta[*c*]-2-quinolone (2b).—Compound **1** (1.00 g) and isobutylene (17 g) in a 700-ml ethanol solution gave 4.0 g of **3** and 7.90 g of **2b**: mp 172.5–173.5° (acetone, 39%); ir (KBr) 1668 cm^{-1} (C=O); uv λ_{max}^{EtOH} 259 mμ (ε 8830); nmr ($CDCl_3$) δ 9.59 (brs, 1, NH), 6.95 (m, 4, ArH), 3.45 (m, 2, cyclobutane, CHCH), 2.34 (m, 2, cyclobutane CH_2), and 1.27 and 0.86 ppm (2 s, 6, 2 CH_3).

5,5-Diethyl-3,6-dihydrocyclobuta[*c*]-2-quinolone (2c).—Compound **1** (6.0 g) and 2-ethyl-1-butene (34.8 g) in a 700-ml ethanol solution gave 3.0 g of **3** and 4.61 g of **2c**: mp 152–153° (acetone, 35%); ir (KBr) 1663 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.81 (brs, 1, NH), 7.00 (m, 4, ArH), 3.54 (m, 2, cyclobutane, CHCH), 2.28 (m, 2, cyclobutane CH_2), 1.65 (q, 2, CH_2CH_3), 1.25 (q, 2, CH_2CH_3), 0.93 (t, 3, CH_3), and 0.60 ppm (t, 3, CH_3).

5,5-Dimethoxy-3,6-dihydrocyclobuta[*c*]-2-quinolone (2d).—Compound **1** (100 mg) and dimethyl ketene acetal[14] (650 mg) in 25 ml of N,N-dimethylacetamide gave 170 mg of **2d**: mp 167–168.5° (acetone, 40%); ir (KBr) 1666 cm^{-1} (C=O); nmr ($CDCl_3$)[23] δ 9.73 (brs, 1, NH), 7.04 (m, 4, ArH), 3.95 (d, 1, J_{AB} = 9.56 Hz, cyclobutane CHCH), 3.32, 3.05 (2 s, 6, 2 OCH_3), 3.3–2.85 (m, 1, cyclobutane CHCH, hidden under OCH_3), and 2.83–2.50 ppm (d, 2, cyclobutane CH_2).

5-Methoxy-3,6-dihydrocyclobuta[*c*]-2-quinolone (2e).—Compound **1** (10.0 g) and vinyl methyl ether (24.9 g) in a 700-ml ethanol solution gave 3.50 g of **3** and 9.1 g of **2e** (vpc indicated two adducts with t_R 29.7 and 36.2 min, *T* 160°, in a 2:1 ratio): mp 124–135° (acetone, 33%); ir (KBr) 1661 cm^{-1} (C=O); nmr ($CDCl_3$) δ 10.13, 9.92 (2 brs, 2, 2 NH), 7.08 (m, 8, ArH), 3.31, 3.25 (2 s, 6, 2 OCH_3), and 4.42–2.0 ppm (brm, 10, cyclobutane CHCH and CH_2). After three recrystallizations, vpc indicated one isomer (t_R 29.7 min): mp 149.5–151° (acetone, 4%); ir (KBr) 1661 cm^{-1} (C=O); nmr reported in Table V.

(23) The nmr of **2d** was a deceptively simple spectrum; see E. O. Bishop in "Annual Review of NMR Spectroscopy," Vol. I, E. F. Mooney, Ed., Academic Press, New York, N. Y., 1968, pp 125–127.

5-Cyano-3,6-dihydrocyclobuta[*c*]-2-quinolone (2f).—Compound **1** (7.25 g) and acrylonitrile (27.5 g) in a 700-ml ethanol solution gave 3.7 g of **3** and 6.32 g of **2f** [vpc indicated two adducts with t_R 12.6 min, *T* 192° (not separated) and tlc indicated a ratio of 1.4:1]: mp 164–176° (ethanol, 42%); ir (KBr) 1666 cm^{-1} (C=O); nmr (DMSO-d_6) δ 10.20 (brs, 1, NH), 7.17 (m, 4, ArH), and 4.42–2.08 ppm (brm, 5, cyclobutane CHCH and CH_2). Trituration of the original reaction mixture gave 0.95 g (16%) of one isomer (lower R_f, lower t_R) by tlc: shrinks at 215°; mp 229.5–231.5°; ir (KBr) 1666 cm^{-1} (C=O); nmr (DMSO-d_6) reported in Table VI.

5-Acetoxy-3,6-dihydrocyclobuta[*c*]-2-quinolone (2g).—Compound **1** (10.0 g) and vinyl acetate (60 g) in a 700-ml ethanol solution gave 2.2 g of **3** and 1.32 g of **2g**: mp 190.5–192.0° (acetone, 4.4%); ir (KBr) 1729 (acetyl C=O) and 1669 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 9.75 (brs, 1, NH), 7.08 (m, 4, ArH), 5.06 (m, 1, cyclobutane CHCH), 4.18–2.25 (brm, 4, cyclobutane CHCH and CH_2), and 2.09 ppm (s, 3, CH_3). The yield was low because product mixed with polymerized vinyl acetate was difficult to purify.

5-*n*-Butoxy-3,6-dihydrocyclobuta[*c*]-2-quinolone (2h).—Compound **1** (10.0 g) and vinyl *n*-butyl ether (69 g) in a 700-ml ethanol solution gave 2.0 g of **3** and 13.3 g of **2h**: mp 121.5–122.5° (acetone, 40%); ir (KBr) 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.62 (brs, 1, NH), 7.04 (m, 4, ArH), 4.08 (m, 2, cyclobutane CHCH), 3.60–2.0 (brm, 5, cyclobutane CHCH, CH_2, and OCH_2), and 1.75–0.60 ppm (brm, 7, $CH_2CH_2CH_3$).

4,4,5,5-Tetrachloro-3,6-dihydrocyclobuta[*c*]-2-quinolone. (2i).—Compound **1** (7.25 g) and tetrachloroethylene (82.9 g) in a 700-ml N,N′-dimethylacetamide solution gave 0.36 g of **3**, 1.67 g of unreacted **1**, and 11.1 g of **2i**: mp 285.5–287.5° (EtOH, 36%), ir (KBr) 1680 cm^{-1} (C=O); nmr (DMSO-d_6) δ 3.37 (brs, 1, NH), 7.14 (m, 4, ArH), and 4.54 ppm (q, 2, J_{AB} = 10.7 Hz) cyclobutane CHCH).

5,5-Diphenyl-3,6-dihydrocyclobuta[*c*]-2-quinolone (2j).—Compound **1** (1.0 g) and 1,1-diphenylethylene (12.4 g) in a 125-ml ethanol solution gave 0.20 g of **3** and 0.45 g of **2j**: mp 191.5–192.5° (column chromatography followed by recrystallization from acetone, 7%); ir (KBr) 1673 cm^{-1} (C=O); nmr (pyridine-d_5) δ 8.73 (brs, 1, NH), 7.23 (m, 14, ArH), 4.78 (d, 1, J_{AB} = 9.12 Hz, cyclobutane CH-CH), and 4.20–2.42 ppm (brm, 3, cyclobutane CHCH and CH_2). The yield was low because the product decomposed either as it formed or on the column.

3,9-Dihydrobicyclo[3.2.0]heptano[6′,7′-*c*]-2-quinolone (2k).—Compound **1** (10.0 g) and cyclopentene (47 g) in a 700-ml ethanol solution gave 4.6 g of **3** and 8.0 g of **2k**: mp 161° dec (acetone, 38%); ir (KBr) 1668 cm^{-1} (C=O); uv λ_{max}^{EtOH} 258 mμ (ε 8550); nmr ($CDCl_3$) δ 9.23 (brs, 1, NH), 6.98 (m, 4, ArH), and 3.5–1.0 ppm (brm, 10, cyclobutane CHCH and CH_2, aliphatic CH_2).

3,12-Dihydrobicyclo[6.2.0]decano[9′,10′-*c*]-2-quinolone (2l).—Compound **1** (10.0 g) and cyclooctene (76 g) in a 700-ml ethanol solution gave 4.3 g of **3** and 8.70 g of **2l**: mp 166° dec (acetone, 22%); ir (KBr) 1667 cm^{-1} (C=O); nmr ($CDCl_3$): δ 9.47 (brs, 1, NH), 6.98 (m, 4, ArH), and 3.5–0.83 ppm (brm, 16, cyclobutane CHCH and CH_2, aliphatic CH_2).

Registry No.—Carbostyril, 493-62-9; **2a**, 19045-10-4; **2b**, 19045-11-5; **2c**, 23667-19-8; **2d**, 23667-20-1; **2e**, 19045-12-6; **2f**, 23667-22-3; **2g**, 23667-23-4; **2h**, 23667-24-5; **2i**, 23667-25-6; **2j**, 23667-26-7; **2k**, 19399-15-6; **2k′**, 23667-28-9; **2l**, 23667-29-0.

Acknowledgments.—We would like to thank Dr. Lars Skattebøl for many helpful discussions during the course of these experiments. We are deeply indebted to Dr. Earl B. Whipple for his many contributions to the interpretation of the nmr spectra.

Azo Compounds. Investigation of Optically Active Azonitriles[1]

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The resolution of (±)-4,4′-azobis(4-cyanopentanoic acid) and the syntheses of (±)- and (−)-dimethyl 4,4′-azobis(4-cyanopentanoate) are reported. Photochemical decomposition of the (+) acid gives (−)-4-cyanopentanoic acid, whereas similar decomposition of the (+) ester results in no significant optical activity in the reaction products. Mechanistic interpretations of these results are discussed. The kinetics of thermal decomposition of the enantiomers and diastereomers of the azonitriles have been investigated and the ORD and CD data of the corresponding (−) isomers are presented.

For several years, the chemistry of azo compounds has been the subject of intensive study in our laboratories.[1b] Of particular significance has been our interest in the question of whether or not the decomposition of an asymmetric dialkylazonitrile would result in the formation of asymmetric products. In order to explore these possibilities, the syntheses and properties of the first optically active aliphatic azonitriles were investigated. This paper describes the preparation of both enantiomers of 4,4′-azobis(4-cyanopentanoic acid) and of the corresponding dimethyl esters. Photochemical decomposition of (+)-4,4′-azobis(4-cyanopentanoic acid) led to the formation of an optically active disproportionation product, while the decomposition of the (+) ester gave rise to essentially no optical activity in the decomposition products. The difference in decomposition behavior between the (+) acid and the (+) ester is rationalized in terms of a mechanistic pathway involving either of two prestructured intermediates. The rates of thermal decomposition and the activation energies of the various azonitriles have been determined, and their ORD and CD properties are also discussed.

Results and Discussion

***meso*- and (±)-4,4′-Azobis(4-cyanopentanoic acid).**— The procedure of Haines and Waters,[3] with some modification, was used to prepare the two diastereomers of 4,4′-azobis(4-cyanopentanoic acid). The two isomers were separated from each other by virtue of the fact that the *meso* isomer, unlike the racemic compound, is insoluble in 10% aqueous methanol. The procedural modifications involved stirring the mixed acids [*meso* and (±) isomers] in 10% aqueous methanol for 24 hr instead of shaking for 1 hr. This would presumably ensure a more complete separation. The (±) isomer was obtained by refrigeration of the filtrate remaining after isolation of the *meso* isomer. Evaporation of the filtrate under reduced pressure, the method previously employed to obtain the racemic isomer,[3] was avoided to prevent possible contamination of the (±) isomer by concomitant precipitation of any *meso* isomer which may have been in solution. These changes were initiated to guarantee maximum purity of the (±) isomer, because Haines and Waters[3] were unsuccessful in their attempts to resolve this compound with brucine and with strychnine in acetone.

The determination of the amount of *meso* and (±) isomers comprising 4,4′-azobis(4-cyanopentanoic acid) was accomplished by nuclear magnetic resonance spectroscopy. The C-methyl hydrogens and the methylene hydrogens of either of the diastereomers of 4,4′-azobis(4-cyanopentanoic acid) exhibit singlets in their respective nmr spectra, whereas the commercially available acid, which consists of a mixture of two diastereomers, shows a pair of doublets in its nmr spectrum. This phenomenon is attributed to the fact that the methyl and methylene hydrogens of the *meso* isomer and those of the (±) isomers are diastereotopic by external comparison,[4] and are classified as anisochronous[4] because of their chemical-shift nonequivalence.

From the ratio of the average peak areas (integrals were determined by at least three scans in each direction) of the methyl doublet appearing in the nmr spectrum of the mixed acids, the mixture was found to contain 51.6 ± 0.5% *meso* isomer. Haines and Waters,[3] who prepared the mixed acids from a Strecker-type synthesis involving the reaction of levulinic acid with hydrazine sulfate and sodium cyanide, followed by bromine oxidation of the intermediate hydrazine, found by titration analysis that the acid consists of 52% *meso* isomer. The commercially available acid is prepared *via* the same route.[5]

Preparation of the Optically Active Azonitriles.— The resolution of (±)-4,4′-azobis(4-cyanopentanoic acid) was accomplished by fractional crystallization of the diastereomeric salts, employing quinine to separate the enantiomeric pair and acetone as solvent. The (+) and (−) acids were obtained from the corresponding salts by treatment with hydrochloric acid, and the maximum specific rotations ($[\alpha]^{25}D$) were +45.3 and −44.8°, respectively.

Other solvent systems, namely ethyl acetate and ether–methanol (*ca.* 20:1, v/v), were also utilized for the resolution of the (±) isomer.[6] However, with both solvent systems, the yields of the quinine salt of the (+) isomer and the specific rotations of the (+) isomer isolated were not so high as those obtained when acetone was used as solvent.

Resolution of the racemic acid could also be effected by preferential fractional crystallization of the (+)

(1) (a) This is the 48th in a series of papers concerned with the preparation and decomposition of azo compounds; (b) for the previous paper, see C. G. Overberger, J. Reichenthal, and J.-P. Anselme, *J. Org. Chem.*, **35**, 138 (1970).

(2) This paper comprises a portion of the dissertation submitted by D. A. Labianca in partial fulfillment of the requirements for the degree of Doctor of Philosophy at The University of Michigan, 1969.

(3) R. M. Haines and W. A. Waters, *J. Chem. Soc.*, 4256 (1955).

(4) K. Mislow and M. Raban in "Topics in Stereochemistry," Vol. I, N. Allinger and E. L. Eliel, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, pp 1–38.

(5) Aldrich Chemical Co., Inc., Milwaukee, Wis., personal communication, 1968.

(6) D. A. Labianca, B. S. Thesis, Polytechnic Institute of Brooklyn, 1965.

isomer, a procedure which is quite rare.[7] The impure (+) isomer crystallized from a slowly cooled water solution of (±) isomer, and, after two careful recrystallizations of this material from water, (+) isomer of 90% optical purity (based on $[\alpha]^{25}D$ + 45.3°) was obtained. The resolution could be facilitated by seeding the initial water solution of racemic compound with a crystal of (+) isomer. However, the reproducibility of this experiment was found to be dependent on careful control of temperature and on volume of solvent used. Furthermore, the yields of (+) isomer isolated were low, and the procedure was quite tedious. Consequently, the classical resolution with quinine was preferred.

The syntheses of (+)- and (−)-dimethyl 4,4′-azobis(4-cyanopentanoate) were accomplished by esterification of the corresponding (+) and (−) acids with diazomethane. Maximum optical purity was attained in each case after one recrystallization ($[\alpha]^{25}D$ +51.0 and −50.6°, respectively).

The determination of the composition of mixtures of *meso*- and (−)-[8a] dimethyl 4,4′-azobis(4-cyanopentanoate) could also be facilitated by nmr analysis. For these isomeric esters, the methylene hydrogens, in contrast to those of the parent acids, possess nearly identical chemical shifts and are, therefore, not perceptibly anisochronous. However, the C-methyl hydrogens are separated by 2.5 cps, a difference of 1.5 cps from the separation observed (4 cps) for the C-methyl hydrogens of the diastereomeric acids.

Decomposition Studies. A. Photochemical Decomposition of (+)-4,4′-Azobis(4-cyanopentanoic acid).—The photolyses of (+)-4,4′-azobis(4-cyanopentanoic acid) in methanol were conducted at 10, −8, and −20°. For each of the decompositions, the product mixtures exhibited observed rotations whose signs were negative. The results of these experiments are summarized in Table I. It is interesting to note that the amount of optical activity in the product mixtures varies directly with the concentration of azo compound subjected to photolysis. Consideration of the reactions undertaken at 10 and −20°, for example, indicates that the molar concentrations of (+) isomer in each instance differ by *ca.* 41% and that the corresponding observed rotations differ by nearly the same quantity (*ca.* 42%). Furthermore, the data show that temperature does not affect the amount of optical activity exhibited by the product mixtures, at least in the range of temperatures investigated. Similar behavior characterized the photolyzed methanol solutions of the (−) isomer,[6] and, in these cases, the observed rotations were positive.

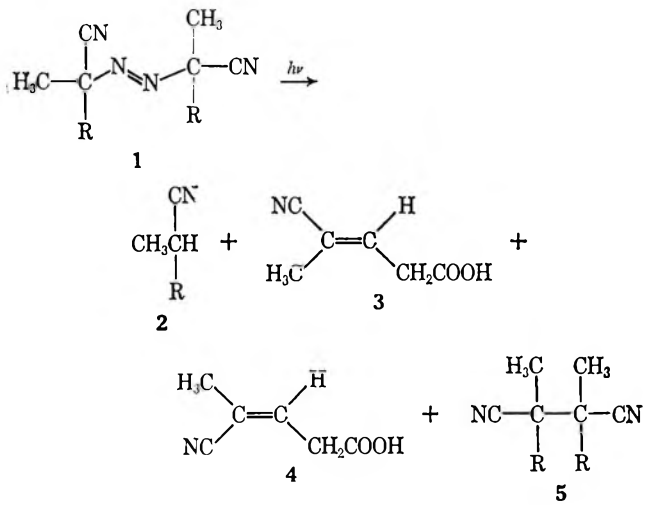
Table I

Variation of Observed Rotation with Concentration for the Photochemical Decomposition of (+)-4,4′-Azobis(4-cyanopentanoic acid)

Wt of azo compound, g	Solvent	Concn, *M*	Temp, °C	Obsd rotation, deg
7.0	MeOH	0.250	10	−0.040
9.6	MeOH	0.342	− 8	−0.050
17.2	MeOH	0.614	−20	−0.096

B. Photolysis Products.—The products resulting from photochemical decomposition of (+)-4,4′-azobis(4-cyanopentanoic acid) at −20° were shown to be those summarized in Scheme I (R = CH_2CH_2COOH).

Scheme I



The predominant isolation procedure involved column chromatography of the photolysis products over silica gel. The isolation of the higher melting isomer (HMDA) of coupled diacid 4,5-dicyano-4,5-dimethyloctane-1,8-dioic acid (**5**) was accomplished by taking advantage of the fact that HMDA precipitates when water is added to the extremely viscous photolysis mixture. Subsequent refrigeration of the filtrate allowed the partial precipitation of the corresponding lower melting isomer (LMDA), the remainder of which was accounted for by chromatographic analysis of a portion of the mixture remaining after removal of the water by lyophilization. In addition, no additional HMDA was isolated by column chromatography. Attempts to distil the liquid disproportionation products (**2**–**4**) from these mixtures under reduced pressure or to isolate them by preparative vapor phase chromatographic analysis were unsuccessful. In both approaches, extensive decomposition occurred and no separations could be effected.

The product distributions in the parent photolysis mixture are summarized in Table II. Both HMDA and LMDA, which are known compounds,[3] were optically inactive and possessed melting points identical with those reported in the literature.[3] (−)-4-Cyanopentanoic acid (**2**, $[\alpha]^{25}D$ −13.1°) and olefins **3** and **4**, which were isolated as a mixture, were the major products. These results are nearly identical with those

Table II

Products of Photolysis of (+)-4,4′-Azobis(4-cyanopentanoic acid) at −20°

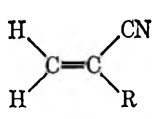
Compd	Yield, %
LMDA	11.7
HMDA	13.1
2	29.8
3 and **4**	33.5

(7) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 78–79.

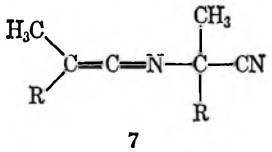
(8) (a) Since enantiomeric conditions are indistinguishable by nmr,[8b] the spectra of the (−) and (+) esters would be identical with that of the (±) ester in achiral solvents; (b) M. Raban and K. Mislow in "Topics in Stereochemistry," Vol. II, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, pp 217–226.

obtained by Haines and Waters,[3] who reported that the coupled products (HMDA and LMDA) constitute the minor fractions of the product mixtures resulting from the thermolyses of *meso*- and (±)-4,4′-azobis(4-cyanopentanoic acid).

It is, of course, also possible that terminal olefin **6** formed during photolysis of the (+)-azo acid, but no evidence was found to indicate the presence of this compound. Ketenimine **7** was not detected. Its



6



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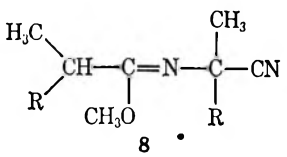
apparent lack of formation was not entirely unexpected, because ketenimines derived from dialkylazonitriles isomerize photochemically (and thermally)[9] to the more stable coupled products similar to LMDA and HMDA. Moreover, these compounds exhibit a characteristic ultraviolet absorption maximum centered at 290 mμ (ϵ_{max} *ca.* 165),[9,10] and the parent photolysis mixture did not show any absorption in this region. The possibility that ketenimine **7** reacted with methanol to give imidate **8** was also considered, but this



8

compound was not detected, nor was there any indication of its presence in the ultraviolet spectrum of the photolysis mixture. Alkyl imidates absorb at *ca.* 255 mμ (ϵ_{max} *ca.* 100).[11]

C. Identification of the Photolysis Products.—The microanalyses and the infrared and nmr spectra of each of the isolated products were consistent with their assigned structures. Both HMDA and LMDA and (−)-4-cyanopentanoic acid (**2**) exhibited the expected absorption in their respective infrared spectra for nonconjugated nitrile groups at *ca.* 2240 cm^{-1} [12] (exact assignments are given in the Experimental Section). The infrared spectrum of the mixture of 4-cyano-*cis*-3-pentenoic acid (**3**) and 4-cyano-*trans*-3-pentenoic acid (**4**) showed a nitrile absorption band at 2225 cm^{-1}, which is characteristic of α,β-unsaturated alkylnitriles.[12] Moreover, the carbon–carbon double-bond-stretching frequency of this mixture appeared at 1635 cm^{-1}, in agreement with the expected range of absorption for trisubstituted alkenes, one substituent of which is a nitrile group.[13]

Certain salient features of the nmr assignments for each of the compounds under consideration are also worthy of note. The nmr spectra (CF_3COOH) of HMDA and LMDA exhibited the expected singlets for the C-methyl hydrogens of these isomers at τ 8.33 and 8.35, respectively, and the methyl absorption [$(CD_3)_2CO$] at τ 8.90 of (−)-4-cyanopentanoic acid (**2**) was split into the anticipated doublet (J = 6.5 cps) by the corresponding methine hydrogen. The difference in chemical shifts for the diastereotopic C-methyl groups in HMDA and LMDA were quite negligible, so that the nmr spectrum of the mixed isomers was nearly identical with those of the individual isomers. It is also interesting that, in contrast to the *meso*- and (±)-azo compounds, the methylene hydrogens of HMDA and LMDA were characterized by multiplets rather than by singlets in their respective nmr spectra, thereby indicating that the absence of the azo linkage gives rise to a significant difference in chemical environment between both pairs of methylene hydrogens in each of the coupled products. Furthermore, the methylene hydrogens of the two isomers of the coupled diacid failed to exhibit any perceptible chemical-shift nonequivalence.

The components of the olefinic mixture were also readily identified by nmr [$(CD_3)_2CO$]. Of particular significance in the spectrum of this mixture was the observation that the coupling constant (J = 3 cps) of the doublet at τ 8.05 assigned to the C-methyl hydrogens of *cis* olefin **3** was, as expected, larger than that (J = 1 cps) of the doublet at τ 7.94 assigned to the methyl group of *trans* olefin **4**. Both the absolute and relative magnitudes of these coupling constants are consistent with the fact that in *cis* olefin **3** the methyl group is *trans* to the vinyl hydrogen (larger coupling constant[14]) and in *trans* olefin **4** the methyl group and the vinyl hydrogen are *cis* to each other (smaller coupling constant[14]). Integration of both doublets indicated that the *cis* and *trans* olefins were present in the mixture in equal amounts.

The ORD spectrum of (−)-4-cyanopentanoic acid (**2**) in methanol was also of some assistance in the identification of this compound. The ORD curve of the photolyzed mixture of (+)-4,4′-azobis(4-cyanopentanoic acid) exhibited a negative Cotton effect, with the first extremum at 225 mμ, which was assigned to the asymmetrically perturbed carboxyl group of the optically active product. Compound **2** gave a similar curve ([M] − 352°), thereby confirming the source of optical activity in the parent product mixture.

D. Photochemical Decomposition of (+)-Dimethyl 4,4′-Azobis(4-cyanopentanoate).—The photochemical decompositions of the (+) ester were undertaken at −20 and −50° in tetrahydrofuran. The reactions were not conducted in methanol because of the insolubility of the ester in this solvent at the indicated temperatures. Both photolyses gave about a 70% yield of an optically inactive (at the sodium D line and in the 450[15]–200-mμ range) mixture of two isomers (LMDE and HMDE) of coupled diester dimethyl 4,5-dicyano-4,5-dimethyloctane-1,8-dioate. Furthermore, the photolyzed solutions showed no optical activity at the sodium D line and the ORD spectra of these solutions in the 450[15]–290-mμ range and of the liquid products resulting from both decompositions in the 300–208-mμ range gave no indication of significant activity. The ORD spectra of the tetrahydrofuran solutions could not be determined at lower wavelengths because of the lack of transparency of the solvent below 290 mμ.

(9) J. R. Fox and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 4031 (1964).
(10) G. S. Hammond, O. D. Trapp, R. T. Keyes, and D. L. Neff, *ibid.*, **81**, 4878 (1959).
(11) "Handbook of Organic Structural Analysis," Y. Yukawa, Ed., W. A. Benjamin, Inc., New York, N. Y., 1965, p 22.
(12) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 37.
(13) D. G. I. Felton and S. F. D. Orr, *J. Chem. Soc.*, 2170 (1955).
(14) Reference 12, p 99.
(15) Preliminary experiments indicated the absence of optical activity above 450 mμ.

The mixture of LMDE and HMDE was separated from the unidentified liquid disproportionation products by preparative glpc analysis and by distillation of the liquid products from the reaction mixtures. The latter procedure was considerably less time consuming. A partial separation of the mixture of coupled diesters into both diastereomers was effected by vacuum sublimation. The infrared and nmr spectra of the impure isomers and of the isomeric mixture were essentially indistinguishable from the corresponding spectra of analytically pure LMDE and HMDE prepared by esterification of LMDA and HMDA, respectively, with diazomethane.

E. Mechanism of Decomposition.—In recent years, several investigations concerned with studies of the stereochemical course of the decomposition of azo compounds have been conducted. Bartlett and McBride[16] have reported that the photolysis of *meso*- and of predominantly (±)-azobis(2-phenyl-3-methyl-2-butane) in methylcyclohexane glass at −196° gave only *meso*-3,4-diphenyl-2,3,4,5-tetramethylhexane (TMDPH) and mostly (±)-TMDPH, respectively. From these experiments, it was concluded that the two radicals produced in a frozen medium under photochemical conditions have the properties anticipated for a radical pair in a cage in which the process of recombination or disproportionation becomes faster than random orientation of the radicals.

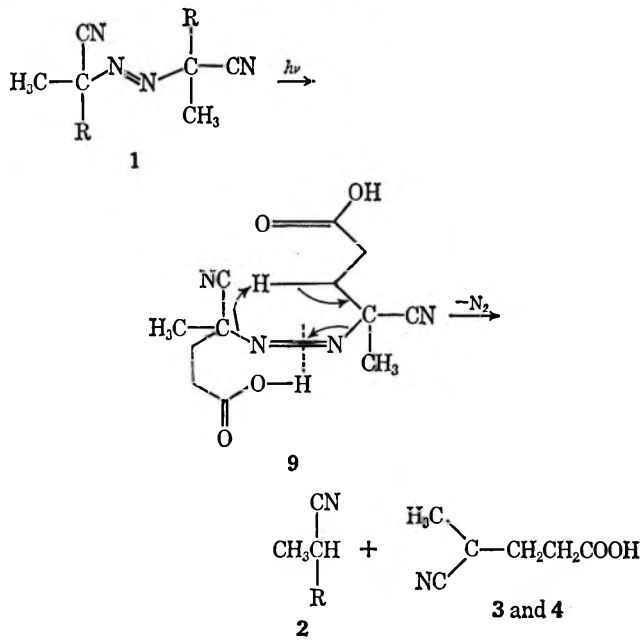
In contrast to these results, Greene[17a-c] found, quite recently, that, of the 28% yield of *meso*- and non-*meso*-2,3-diphenylbutanes obtained from the thermal decomposition of optically pure azobis-α-phenylethane in benzene at 105° in the presence of 2-methyl-2-nitrosopropane as scavenger, only a small amount of the non-*meso* coupled product was optically active. These observations were considered to be indicative of significant progress toward complete randomization of the thermally generated radicals within the solvent cage prior to recombination. The results of this work are in excellent agreement with those of Kopecky and Gillan,[17d] who studied the decomposition of racemic and optically active 1,1′-diphenyl-1-methylazomethane.

The decomposition of an optically active six-membered cyclic azo compound has been reported by Bartlett and Porter[18] to give an optically active coupled product. However, in this report, which was concerned primarily with the thermolyses and with the direct and sensitized photolyses of the *meso* and (±) cyclic azo compounds, the details of the optically active work were not given.

The formation of optically active decomposition products derived from optically active peroxides has also received considerable attention.[19] In these cases, some of the interpretations presented were similar to those previously mentioned.

The foregoing, brief mechanistic discussions facilitate the consideration of somewhat related arguments to explain the formation of (−)-4-cyanopentanoic acid (2) during the photochemical decomposition of (+)-4,4′-azobis(4-cyanopentanoic acid). The formation of optically inactive coupled products (LMDA and HMDA) and an optically active disproportionation product (2) might be rationalized in terms of a prestructured intermediate (9, Scheme II), the formation of which would depend on the photochemically induced isomerization of the *trans*-azo bond of the optically active acid to the corresponding *cis*-azo linkage,[20a,b] which would be stabilized by hydrogen bonding[20c] with the proton of one of the carboxyl groups. Models indicate that structure 9 is feasible. Subsequent elimination of nitrogen followed by rapid abstraction of a hydrogen atom by the intermediate radical within the solvent cage would give (−)-2 and the two isomers of 4-cyano-3-pentenoic acid (3 and 4). Since the distance between the two radicals generated from intermediate 9 is greater than that separating one of the radicals from the hydrogen atom to be abstracted, the coupling of these radicals would be expected to require more time than the disproportionation process. As a consequence of this time factor, the intermediate radicals could achieve complete random orientation prior to their recombination and, accordingly, optically inactive coupled products would form. The elimination of nitrogen might also occur to some extent *via* a concerted process, as depicted in Scheme II.

SCHEME II



This mechanism would also explain the insignificant amount of optical activity exhibited by product mixtures resulting from the thermal decomposition of optically active azo acid,[6] since isomerization of alkylazo compounds has not been detected during thermolysis. Furthermore, the thermally generated radicals would be expected to become randomly oriented at a considerably faster rate[17a-c] than the corresponding

(16) P. D. Bartlett and J. M. McBride, *Pure Appl. Chem.*, **15**, 89 (1967).

(17) (a) F. D. Greene, Massachusetts Institute of Technology, personal communication, 1968; (b) F. D. Greene and M. A. Berwick, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, No. 0112; (c) F. D. Greene, M. A. Berwick, and J. C. Stowell, *J. Amer. Chem. Soc.*, **92**, 867 (1970); (d) K. R. Kopecky and T. Gillan, *Can. J. Chem.*, **47**, 2371 (1969).

(18) P. D. Bartlett and N. A. Porter, *J. Amer. Chem. Soc.*, **90**, 5317 (1968).

(19) (a) S. Oae, T. Kashiwagi, and S. Kozuka, *Chem. Ind.* (London), 1694 (1965), and references cited therein; (b) H. M. Walborsky and C. J. Chen, *J. Amer. Chem. Soc.*, **89**, 5499 (1967).

(20) (a) R. F. Hutton and C. Steel, *ibid.*, **86**, 745 (1964), and references cited therein; (b) I. I. Abram, G. S. Milne, B. S. Solomon, and C. Steel, *ibid.*, **91**, 1220 (1969); (c) H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers Inc., New York, N. Y., 1961, pp 328–337.

TABLE III

ORD, CD, AND UV DATA FOR (−)-4,4′-AZOBIS(4-CYANOPENTANOIC ACID) AND (−)-DIMETHYL 4,4′-AZOBIS(4-CYANOPENTANOATE)

Compd	Solvent	Concn, *M*		ORD		CD		Uv	
		ORD, CD	Uv	λ_{extr}, mμ	[M], deg	λ_{max}, mμ	$\Delta\epsilon_{max}$	λ_{max}, mμ	ϵ_{max}
(−)-4,4′-Azobis-(4-cyanopentanoic acid)[a]	Methanol	0.0178	0.0177	375	−1682				
				353	0	349	−0.84	348	20
				327	+2298				
				227	+1289				
(−)-Dimethyl 4,4′-azobis(4-cyanopentanoate)[b]	Methanol	0.0170	0.0161	375	−2173				
				352	0	347	−0.97	348	19
				328	+2760				
				225	+1468				
(−)-4,4′-Azobis-(4-cyanopentanoic acid)[a]	Dioxane	0.0185	0.0167	374	−1840				
				348	0	350	−0.73	347	18
				325	+1515				
				230	+ 758				
(−)-Dimethyl 4,4′-azobis(4-cyanopentanoate)[b]	Dioxane	0.0173	0.0155	373	−1793				
				351	0	347	−0.87	347	18
				326	+2430				
				225	+1620				

[a] $[\alpha]^{25}D$ − 44.8° (*c* 2.463, methanol), 98.9% optically pure based on $[\alpha]^{25}D$ + 45.3° for the (+) isomer. [b] $[\alpha]^{25}D$ − 49.9° (*c* 3.802, methanol), 97.8% optically pure based on $[\alpha]^{25}D$ +51.0° for the (+) isomer.

radicals generated at low temperatures under photochemical conditions.[16]

The question as to why the photochemical decomposition of optically active dimethyl 4,4′-azobis(4-cyanopentanoate) gives rise to larger amounts of coupled products (LMDE and HMDE) than the photolysis of the optically active azo acid and to no significant optical activity in the resulting product mixtures must also be considered. Perhaps an intermediate similar to **9** could not be generated in this case because the ester functions would be incapable of stabilizing the *cis*-azo linkage by hydrogen bonding.

An alternate explanation for these results would depend upon the formation of an intermediate involving hydrogen bonding between the carboxyl substituents of the optically active acid.[21] Models indicate that within such a 13-membered cyclic structure in which the configuration of the azo linkage is *cis*, a six-membered cyclic transition state similar to that depicted in **9** is possible. Accordingly, hydrogen abstraction by the intermediate radical is again more favorable than the corresponding coupling process because of the closer proximity of the hydrogen atom to the abstracting radical. However, on the basis of the available data, no definite choice can yet be made between this structure and structure **9**.

ORD and CD Properties of the Optically Active Azonitriles.—The first optically active azo alkane for which ORD and CD data have been reported in 2,2′-azobis(2-phenylbutane).[22] The ORD curve of the (+) isomer of this compound was determined in isooctane; the positive Cotton effect curve exhibited a peak at 412 mμ ([M] + 1420°) and a trough at 355 mμ ([M] − 2250°). Bartlett and McBride[16] found that the optical rotatory dispersion of (+)-azobis(2-phenyl-3-methyl-2-butane) is quite similar to that of (+)-2,2′-azobis(2-phenylbutane),[22] although the rotation in the latter case is stronger.

The optical rotatory dispersions of (−)-4,4′-azobis-(4-cyanopentanoic acid) and of (−)-dimethyl 4,4′-azobis(4-cyanopentanoate) in dioxane and in methanol were investigated. Both compounds gave the expected negative Cotton effect curve owing to the asymmetrically perturbed azo group. Another salient feature of both sets of spectra is a second Cotton effect, with the first extremum appearing in the region 225–230 mμ. This second effect is due to the asymmetrically perturbed carbonyl function of the carboxyl and carboxylate groups, respectively. The magnitude of this Cotton effect is significantly smaller than that attributed to the azo group because the carboxyl and carboxylate moieties are further removed from the asymmetric carbon atoms of the respective azo compounds. These data as well as the corresponding ultraviolet absorption data are summarized in Table III.

The CD spectrum of (+)-2,2′-azobis(2-phenylbutane)[22] was found to be quite interesting. Kosower and Severn[22] observed that the circular dichroism of this compound changes sign in the region of the n → π* absorption.[23a] The same result, with opposite sign, was exhibited by the corresponding (−) isomer. The possibility that this apparent splitting is due to two separate transitions, $n_+ \rightarrow \pi^*$ and $n_- \rightarrow \pi^*$,[23a] with the latter having a small rotational strength and a sign opposite to that of the main $n_+ \rightarrow \pi^*$ bond, was postulated. However, on the basis of theoretical calculations by Robin, Hart, and Kuebler,[23b] Huang and Kosower[24a] recently narrowed the assignment to that of a single electronic transition, $n_+ \rightarrow \pi^*$, with the observed change of sign being attributed to the presence of two *vibronic* states, each with some $n_+ \rightarrow \pi^*$ electronic state but having accompanying vibrations of different symmetries. It is interesting to note that Robin and coworkers[23b] indicate that Kosower informed them that the circular dichroism spectrum of a derivative of

(21) R. G. Lawton, The University of Michigan, personal communication, 1969.

(22) E. M. Kosower and D. J. Severn, *Tetrahedron Lett.*, 3125 (1966).

(23) (a) The originating orbital, n_+, is the antibonding combination of the two nonbonding orbitals on the azo nitrogens, and n_- is the corresponding bonding combination;[23b] (b) M. B. Robin, R. R. Hart, and N. A. Kuebler, *J. Amer. Chem. Soc.*, **89**, 1564 (1967).

(24) (a) P. C. Huang and E. M. Kosower, *ibid.*, **90**, 2367 (1968). (b) The derivative is probably optically active 2,2′-azobis(2-cyclohexylbutane); see D. J. Severn and E. M. Kosower, *ibid.*, **91**, 1710 (1969).

TABLE IV
RATE CONSTANTS AND ACTIVATION ENERGIES FOR THE THERMAL DECOMPOSITION OF AZONITRILES IN N,N-DIMETHYLACETAMIDE

Compd	$[\alpha]^{25}D$, deg (c, solvent)	Optical purity, %	k, min^{-1}	Decompn temp, °C	E_a, kcal/mol
meso-4,4′-Azobis-(4-cyanopentanoic acid)	...	...	8.02×10^{-3}	77.6	31.9
			2.23×10^{-2}	85.3	
			4.32×10^{-2}	90.9	
			1.22×10^{-1}	99.8	
(±)-4,4′-Azobis-(4-cyanopentanoic acid)	...	...	9.20×10^{-3}	77.9	32.1
			2.48×10^{-2}	85.8	
			4.22×10^{-2}	90.1	
			1.26×10^{-1}	99.1	
(+)-4,4′-Azobis-(4-cyanopentanoic acid)	+44.5 (4.768, methanol)	98.2[a]	9.36×10^{-3}	78.0	32.1
			2.44×10^{-2}	85.4	
			4.21×10^{-2}	90.0	
			1.21×10^{-1}	99.0	
(−)-4,4′-Azobis-(4-cyanopentanoic acid)	−43.1 (4.602, methanol)	95.1[a]	9.10×10^{-3}	77.7	32.1
			2.62×10^{-2}	86.0	
			4.42×10^{-2}	90.5	
			1.35×10^{-1}	99.7	
meso-Dimethyl 4,4′-azobis(4-cyanopentanoate)	...	...	8.60×10^{-3}	77.9	32.0
			2.27×10^{-2}	85.0	
			4.10×10^{-2}	90.2	
			1.24×10^{-1}	99.7	
(+)-Dimethyl 4,4′-azobis(4-cyanopentanoate)	+49.7 (3.880, methanol)	97.5[b]	8.83×10^{-3}	77.6	31.9
			2.43×10^{-2}	85.9	
			4.16×10^{-2}	90.0	
			1.23×10^{-1}	99.2	
(−)-Dimethyl 4,4′-azobis(4-cyanopentanoate)	−49.9 (3.802, methanol)	97.8[b]	8.99×10^{-3}	77.9	31.9
			2.35×10^{-2}	85.4	
			4.19×10^{-2}	90.2	
			1.19×10^{-1}	99.0	

[a] Based on $[\alpha]^{25}D$ +45.3° for the (+) isomer. [b] Based on $[\alpha]^{25}D$ +51.0° for the (+) isomer.

optically active 2,2′-azobis(2-phenylbutane)[22] shows only one band in the n → π* region. However, the structure of this derivative was not specified.[24b]

To determine whether similar behavior is exhibited by optically active 4,4′-azobis(4-cyanopentanoic acid) and by the corresponding dimethyl ester, the circular dichroisms of the (−) isomers of both compounds were determined in dioxane and in methanol. The CD curves possessed a single absorption in the n → π* region (Table II), and, on the basis of the conclusions arrived at by Robin and coworkers[23] and by Huang and Kosower,[24a] this band can be assigned to the $n_+ \rightarrow \pi^*$ transition.

Kinetics.—The rates of thermal decomposition of the various isomers of 4,4′-azobis(4-cyanopentanoic acid) and of dimethyl 4,4′-azobis(4-cyanopentanoate) were determined at four temperatures. The volume of nitrogen evolved during specified time intervals was determined from the displacement of mercury in a gas buret, and the rate constant, k, was calculated from the product of 2.303 and the slope of a plot of log $[v_\infty/(v_\infty - v_t)]$ *vs.* time. Activation energies were obtained from the slopes of plots of ln k *vs.* $1/T \times 10^3$. Each reaction investigated was found to exhibit first-order kinetics. The rate data are summarized in Table IV.

Small differences in rate constants for optical isomers of the same compound can be attributed to slight differences in decomposition temperature for corresponding runs. The activation energies are quite similar to those reported for related azonitriles.[25]

Experimental Section

Melting points are uncorrected. Microanalyses were performed by Alfred Bernhardt Mikroanalytishes Laboratorium, Mülheim (Ruhr), West Germany, and by Spang Microanalytical Laboratory, Ann Arbor, Mich. Nuclear magnetic resonance

(25) "Polymer Handbook," J. Brandrup and E. H. Immergut, Ed., John Wiley & Sons, Inc., New York, N. Y., 1966, pp 113–118.

spectra were obtained on a Varian Associates Model A-60 spectrometer using tetramethylsilane as internal standard, except where noted otherwise. Infrared spectra were recorded on a Perkin-Elmer Model 521 spectrophotometer and on a Perkin-Elmer Model 257 spectrophotometer. Ultraviolet absorption data were obtained with a Beckman Model DU spectrophotometer, and the ORD and CD measurements were made with a Jasco ORD/CD/UV-5 spectropolarimeter at room temperature. All observed rotations at the sodium D line were determined with a Bendix–Ericsson Type 143A polarimeter (0.1-dm cell) at 25°, and, in those instances where specific rotations are listed without reference to sample concentration, the reader should assume that the concentration for the specific rotation in question was given in an earlier experiment. Refractive indices were measured with an Abbe (Spencer 1747) refractometer. All preparative and analytical glpc was performed on a Varian Aerograph Model A-700 with a 20 ft × 0.375 in. aluminum column packed with 20% SE-30 silicone gum rubber on 60–80 mesh Chromosorb W. Petroleum ether refers to the fraction boiling at 30–60°.

Separation of *meso*- and (±) Isomers of 4,4′-Azobis(4-cyanopentanoic acid).—The procedure of Haines and Waters,[3] somewhat modified, was utilized. A slurry of 360 g (1.28 mol) of 4,4′-azobis(4-cyanopentanoic acid) (Aldrich) in 21,600 ml of 10% aqueous methanol (60 ml per gram of mixed acids), distributed between two 6000-ml erlenmeyer flasks, was stirred for 24 hr, after which time it was filtered to give crude *meso* isomer. This isomer was dissolved at 75–80° in *ca.* 12,000 ml of water, and cooling of the solution to room temperature afforded 114.5 g (*ca.* 60% yield)[26] of colorless needles: mp 134.5–135° dec (lit.[3] mp 128° dec); ν_{max}^{Nujol} 2255 (C≡N) and 1715 cm^{-1} (C=O); λ_{max}^{MeOH} 350 mμ (ε 18); nmr (CF_3COOH) τ 8.17 (singlet, 6 H, CCH_3) and 7.37 (singlet, 8 H, CH_2CH_2COOH).

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.43; H, 5.75; N, 19.99. Found: C, 51.75; H, 5.92; N, 19.96.

Upon cooling the filtrate at −3° for 24 hr, crude (±) isomer precipitated. Recrystallization from *ca.* 4000 ml of water maintained at 60–65° gave 86.5 g (*ca.* 50% yield)[26] of colorless solid: mp 117–118° dec (lit.[3] mp 110–111° dec); ν_{max}^{KBr} 2245 (C≡N) and 1715 cm^{-1} (C=O); λ_{max}^{MeOH} 349 mμ (ε 19); nmr (CF_3COOH) τ 8.24 (singlet, 6 H, CCH_3) and 7.32 (singlet, 8 H, CH_2CH_2COOH).

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.43; H, 5.75; N, 19.99. Found: C, 51.56; H, 5.80; N, 19.87.

Resolution of (±)-4,4′-Azobis(4-cyanopentanoic acid) with Quinine.—A mixture of 83 g (0.296 mol) of (±)-4,4′-azobis(4-cyanopentanoic acid) and 192.2 g (0.592 mol) of quinine was added portionwise and with stirring to *ca.* 6000 ml of acetone maintained at room temperature. Stirring was continued for 2 hr after the addition of the mixture to ensure complete precipitation of the quinine salt of the (+) isomer. Subsequent filtration followed by several washings of the salt with 2000-ml portions of acetone gave 180.9 g (61% yield, theoretical yield 50%) of impure quinine salt of (+) isomer, mp 120–123° dec. This salt was added portionwise and with stirring to an excess of 4 *N* hydrochloric acid (275–300 ml) kept at 0–5°. The resulting suspension was cooled at −3° for 7 hr and then filtered to give 47.5 g (0.169 mol) of impure (+) isomer, mp 119–122° dec. A further resolution of this isomer, conducted in the same manner as the first, utilizing 110 g (0.339 mol) of quinine and *ca.* 5000 ml of acetone, gave 110 g (40% yield based on the first resolution) of analytically pure quinine salt of the (+) isomer, $[\alpha]^{25}D$ −131° (*c* 3.056, methanol), mp 129–130° dec. Recrystallization of this salt from large volumes of acetone did not change its melting point or specific rotation.

Anal. Calcd for $C_{52}H_{64}N_8O_3$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.35; H, 7.03; N, 12.19.

Generation of the (+) isomer by treatment of this salt with 4 *N* hydrochloric acid in the same fashion as previously described and subsequent recrystallization of this isomer from water maintained at 60–65° gave 23 g (55.4% overall yield) of colorless platelets, $[\alpha]^{25}D$ +45.3° (*c* 3.037, methanol), mp 130–131° dec. Further recrystallization of the (+) isomer from water did not alter its melting point or specific rotation: ν_{max}^{Nujol} 2255 (C≡N) and 1715 cm^{-1} (C=O); λ_{max}^{MeOH} 348 mμ (ε 20); nmr (CF_3COOH) τ 8.24 (singlet, 6 H, CCH_3) and 7.32 (singlet, 8 H, CH_2CH_2COOH).

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.43; H, 5.75; N, 19.99. Found: C, 51.60; H, 5.81; N, 19.85.

(26) The indicated yield was calculated on the basis of the approximate theoretical composition of the mixed acids as determined by nmr analysis.

The combined acetone filtrate was evaporated under reduced pressure at room temperature, and to the remaining quinine salt of (−) isomer kept at 0–5° was added, with stirring, excess 4 *N* hydrochloric acid (275–300 ml). The resulting suspension was cooled at −3° for 10 hr, after which time filtration and subsequent recrystallization of the (−) isomer from water at 60–65° gave 20 g (48.2% overall yield) of colorless platelets, $[\alpha]^{25}D$ −44.8° (*c* 2.463, methanol), mp 130–131° dec. No change in the melting point or specific rotation could be effected by further recrystallization. The ORD and CD data for the (−) isomer are summarized in Table III; ν_{max}^{Nujol} 2255 (C≡N) and 1715 cm^{-1} (C=O); λ_{max}^{MeOH} 348 mμ (ε 20); nmr (CF_3COOH) τ 8.24 (singlet, 6 H, CCH_3) and 7.32 (singlet, 8 H, CH_2CH_2COOH).

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.43; H, 5.75; N, 19.99. Found: C, 51.61; H, 5.89; N, 19.84.

Resolution of (±)-4,4′-Azobis(4-cyanopentanoic acid) by Fractional Crystallization.—(±)-4,4′-Azobis(4-cyanopentanoic acid) (33 g) was dissolved in *ca.* 1000 ml of water at 60–65°, and slow cooling of the resulting solution to room temperature afforded 25 g of a mixture of racemic isomer (colorless solid) and impure (+) isomer (colorless platelets), $[\alpha]^{25}D$ +1.36° (*c* 2.980, methanol), mp 120–122° dec. The platelets (5.5 g) were separated from the racemic isomer with tweezers and subjected to slow recrystallization from *ca.* 400 ml of water as previously described; after 4 hr, 1.5 g of colorless platelets formed, $[\alpha]^{25}D$ +8.53° (*c* 2.355, methanol), mp 125–127° dec. A third recrystallization of this material from *ca.* 250 ml of water gave 0.65 g of colorless platelets, $[\alpha]^{25}D$ +40.8° (*c* 2.875, methanol), 90% optically pure based on $[\alpha]^{25}D$ +45.3°, mp 129–130° dec.

Syntheses of (+)- and (−)-Dimethyl 4,4′-Azobis(4-cyanopentanoate).—A solution of diazomethane in ether was prepared from 35 g (0.340 mol) of N-nitroso-N-methylurea according to the method of Eistert[27a] and distilled as described by Arndt.[27b] This solution was added slowly to a stirred slurry of 8.35 g (29.8 mmol) of (+)-4,4′-azobis(4-cyanopentanoic acid), $[\alpha]^{25}D$ +45.3°, in ether maintained at 0–5°. The resulting yellow solution was stirred for 1 hr, after which time the ether was removed under vacuum and the residual colorless solid was dissolved in ethanol. Refrigeration of the solution at −20° for 10 hr allowed the precipitation of 7.8 g (85% yield) of colorless needles, $[\alpha]^{25}D$ +51.0° (*c* 2.970, methanol), mp 72–73°. Further recrystallization from ethanol failed to increase the specific rotation and the melting point: ν_{max}^{Nujol} 2240 (C≡N) and 1735 cm^{-1} (C=O); λ_{max}^{MeOH} 348 mμ (ε 19); nmr (DMSO-d_6) τ 8.37 (singlet, 6 H, CCH_3), 7.61 (singlet, 8 H, $CH_2CH_2COOCH_3$), and 6.42 (singlet, 6 H, $COCH_3$).

Anal. Calcd for $C_{14}H_{20}N_4O_4$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.53; H, 6.48; N, 18.07.

The (−) isomer was prepared in a similar fashion from 1 g (3.57 mmol) of (−)-4,4′-azobis(4-cyanopentanoic acid), $[\alpha]^{25}D$ −44.8°, utilizing a solution of diazomethane prepared from 17 g (0.165 mol) of N-nitroso-N-methylurea. Recrystallization from ethanol at −20° gave 0.91 g (83% yield) of colorless needles, $[\alpha]^{25}D$ −50.6° (*c* 3.104, MeOH), mp 72–73°, and no change in these data could be effected by further recrystallization. The ORD and CD data for the (−) isomer are listed in Table III; ν_{max}^{Nujol} 2240 (C≡N) and 1735 cm^{-1} (C=O); λ_{max}^{MeOH} 348 mμ (ε 19); nmr (DMSO-d_6) τ 8.37 (singlet, 6 H, CCH_3), 7.61 (singlet, 8 H, $CH_2CH_2COOCH_3$), and 6.42 (singlet, 6 H, $COOCH_3$).

Anal. Calcd for $C_{14}H_{20}N_4O_4$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.63; H, 6.52; N, 18.26.

Synthesis of *meso*-Dimethyl 4,4′-Azobis(4-cyanopentanoate).—The esterification of 7.5 g (26.8 mmol) of *meso*-4,4′-azobis(4-cyanopentanoic acid) was conducted in the manner described in the preceding experiment, utilizing a solution of diazomethane in ether prepared from 35 g (0.340 mol) of N-nitroso-N-methylurea. The crude ester was dissolved in ethanol and refrigeration of the solution at −20° gave 6.21 g (75.3% yield) of colorless platelets: mp 98–99°; ν_{max}^{Nujol} 2250 (C≡N) and 1735 cm^{-1} (C=O); λ_{max}^{MeOH} 349 mμ (ε 19); nmr (DMSO-d_6) τ 8.32 (singlet, 6 H, CCH_3), 7.62 (singlet, 8 H, $CH_2CH_2COOCH_3$), and 6.43 (singlet, 6 H, $COOCH_3$).

Anal. Calcd for $C_{14}H_{20}N_4O_4$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.52; H, 6.35; N, 18.05.

(27) (a) B. Eistert in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, New York, N. Y., 1948, p 564; (b) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, pp 165, 166.

Synthesis of the Isomers (LMDE, HMDE) of Dimethyl 4,5-Dicyano-4,5-dimethyloctane-1,8-dioate.—The procedure employed was identical with that described for the esterification of (+)- and (−)-4,4′-azobis(4-cyanopentanoic acid). The solutions of diazomethane in ether were prepared from 17 g (0.165 mol) of N-nitroso-N-methylurea. Esterification of 3 g (11.9 mmol) of HMDA[3] and recrystallization of the resulting HMDE from ethanol at −15° gave 2.4 g (72% yield) of colorless needles: mp 136.5–138°; ν_{max}^{Nujol} 2240 (C≡N) and 1740 cm^{-1} (C=O); nmr (internal standard, DSS, DMSO-d_6) τ 8.57 (singlet, 6 H, CCH_3), 7.95 (multiplet, 4 H, $CH_2CH_2COOCH_3$), 7.45 (multiplet, 4 H, $CH_2CH_2COOCH_3$), and 6.38 (singlet, 6 H, $COOCH_3$).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 59.82; H, 7.10; N, 9.98.

Similar treatment of 2.7 g (10.7 mmol) of LMDA[3] gave 2.6 g (86.7% yield) of LMDE as a colorless solid: mp 105.5–107°; ν_{max}^{Nujol} 2240 (C≡N) and 1740 cm^{-1} (C=O); nmr (DSS internal standard, DMSO-d_6) τ 8.57 (singlet, 6 H, CCH_3), 7.95 (multiplet, 4 H, $CH_2CH_2COOCH_3$), 7.47 (multiplet, 4 H, $CH_2CH_2COOCH_3$), and 6.38 (singlet, 6 H, $COOCH_3$).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 59.73; H, 7.15; N, 10.03.

Photochemical Decompositions of (+)-4,4′-Azobis(4-cyanopentanoic acid).—The results of these experiments are summarized in Table I. The samples of (+) acid were dissolved in 100 ml of Spectrograde methanol (Matheson Coleman and Bell) in a Pyrex photolysis cell (*ca.* 240-ml capacity) fitted with a ground-glass joint. The cell was connected to a copper coil surrounded by a Pyrex glass jacket through which circulating water flowed. The coil, in turn, was connected by means of Tygon tubing to the mouth of a Pyrex bottle containing water (*ca.* 2000 ml). An opening at the bottom of the bottle was connected by means of a rubber tubing to a manometer (upper half of a polyethylene wash bottle). The progress of each reaction was followed by the volume of water displaced by the evolved nitrogen, the water being collected in a graduated cylinder. This technique proved to be considerably accurate.

The cell containing the solution of azo compound was placed in a dewar flask (6-in. i.d., 4300-ml capacity) adjacent to a quartz jacket containing a Hanovia 450-W medium-pressure mercury lamp. This dewar flask, containing a thermometer, was filled with ethanol and lined with a copper coil which was connected by means of tygon tubing to the quartz jacket and to another copper coil lining the sides of a second dewar flask (6-in. i.d., 4300-ml capacity). For the reaction at 10°, the second dewar flask was filled with an acetone–ice mixture (replenished *ca.* every 50 min) and the solution of azo compound, 7 g (25.0 mmol), $[\alpha]^{25}D$ +43.7° (*c* 3.531, methanol), 96.7% optically pure based on $[\alpha]^{25}D$ +45.3°, was cooled by circulating ethanol through the entire system. Irradiation of the solution of azo compound was conducted intermittently for 21 hr, during which time quantitative nitrogen evolution occurred. The resulting solution exhibited an observed rotation of −0.040°.

A mixture of methanol–water (*ca.* 50:50 v/v) and Dry Ice was used to cool the circulating ethanol for the reaction at −8°. Quantitative nitrogen evolution occurred after intermittent irradiation of the solution of azo compound, 9.6 g (34.2 mmol), $[\alpha]^{25}D$ +43.7°, for 20 hr and the resulting solution possessed an observed rotation of −0.050°. Similarly, a Dry Ice–methanol mixture was used to cool the circulating ethanol for the photolysis conducted at −20°. The solution of (+) acid, 17.2 g (61.4 mmol), $[\alpha]^{25}D$ +45.3° (*c* 3.107, methanol), was irradiated intermittently for 24 hr, after which time quantitative nitrogen evolution occurred. An observed rotation of −0.096° was exhibited by the photolyzed solution.

Decomposition Products.—The solution photolyzed at −20° was subjected to thin layer chromatography, utilizing a precoated silica gel (polyethylene terephthalate) sheet (Eastman Chromogram Sheet 6060) and methanol as developing solvent. Two nearly overlapping spots, detected by exposing the dried sheet to iodine vapor, appeared in close proximity to the point of initial spotting. These spots were attributed to HMDA and LMDA, respectively, by comparison with authentic samples.[3]

Methanol was removed by rotary evaporation (40°) from the photolyzed solution, and upon addition of 100 ml of water to the product mixture (15.3 g), 2 g (13.1% yield) of HMDA precipitated. Recrystallization of this isomer from dioxane gave colorless needles, mp 207–208° (lit.[3] mp 207–208°). Subsequent cooling of the aqueous filtrate at −3° afforded 0.8 g (5.2% yield) of LMDA, which was recrystallized from water to give a colorless solid, mp 182–183° (lit.[3] mp 182–183°). Samples of LMDA (*c* 3.472, methanol) and of HMDA (*c* 3.768, methanol) exhibited no optical activity at the sodium D line or in the range of 600–210 mμ (ORD):[28] ν_{max}^{KBr} HMDA, 2240 (C≡N) and 1710 cm^{-1} (C=O); LMDA 2240 (C≡N) and 1710 cm^{-1} (C=O); nmr (CF_3COOH) HMDA τ 8.33 (singlet, 6 H, CCH_3), 7.75 (multiplet, 4 H, CH_2CH_2COOH), and 7.15 (multiplet, 4 H, CH_2CH_2COOH); LMDA, τ 8.35 (singlet, 6 H, CCH_3), 7.77 (multiplet, 4 H, CH_2CH_2COOH), and 7.17 (multiplet, 4 H, CH_2CH_2COOH).

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: HMDA C, 57.18; H, 6.38; N, 11.10. LMDA C, 57.00; H, 6.26; N, 11.07.

The remaining aqueous solution was lyophilized (0.025 mm) for 24 hr, and column chromatography (65 × 2.2 cm column) of a 4-g portion of the remaining product mixture (12.4 g) over 160 g of silica gel absorbent (Grace–Davison Chemical, Grade 923) using ether as eluent gave, in the order in which they came off the column, 0.32 g (8% yield) of LMDA [optically inactive at the sodium D line and in the 600–210-mμ range (ORD) (*c* 3.312, methanol)], mp 182–183°, 1.75 g (43.8% yield) of analytically impure (−) acid **2**, $[\alpha]^{25}D$ −9.94° (*c* 3.116, methanol), and 1.65 g (41.3% yield) of a mixture of *cis* and *trans* olefins **3** and **4**, $n^{23}D$ 1.4575. Impure acid **2** was rechromatographed (48 × 2.2 cm column) over 80 g of silica gel and elution with an 80% ether–petroleum ether (v/v) solvent mixture gave 1.47 g (36.8% yield based on the mixture added to the first column)[29] of **2**: $[\alpha]^{25}D$ −13.1° (*c* 3.112, methanol); $[M]_{225}$ −352° (*c* 0.3107, methanol); $n^{28}D$ 1.4476; ν_{max}^{neat} **2** 2245 (C≡N) and 1715 cm^{-1} (C=O); **3** and **4**, 2225 (C≡N), 1710 (C=O), and 1635 cm^{-1} (C=C); nmr [$(CD_3)_2C$=O], **2**, τ 8.90 (doublet, 3 H, J = 6.5 cps, CCH_3), 8.22 (multiplet, 2 H, CH_2CH_2COOH), 7.51 (multiplet, 2 H, CH_2CH_2COOH), 5.39 (multiplet, 1 H, CH), and −1.48 (singlet, 1 H, COOH); **3** and **4**, τ 8.05 and 7.94 (two doublets, 6 H, J = 3 and 1 cps, respectively, CCH_3), 6.09 and 5.97 (two doublets, 4 H, J = 9.5 and 10 cps, respectively, CH_2COOH), 3.95 (multiplet, 2 H, C=CH), and −1.62 and −1.73 (two singlets, 2 H, COOH).

Anal. Calcd for $C_6H_9NO_2$ (**2**): C, 56.68; H, 7.13; N, 11.02. Found: C, 56.89; H, 6.98; N, 11.06. Calcd for $C_6H_7NO_2$ (**3** and **4**): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.36; H, 5.39; N, 10.97.

Photochemical Decomposition of (+)-Dimethyl 4,4′-Azobis(4-cyanopentanoate) at −20°.—A solution of 6.7 g (21.7 mmol) of (+)-dimethyl 4,4′-azobis(4-cyanopentanoate), $[\alpha]^{25}D$ +50.8° (*c* 1.000, methanol), in 100 ml of tetrahydrofuran (freshly distilled from $LiAlH_4$) was intermittently irradiated, as described for the (+) acid, for 38 hr, after which time quantitative nitrogen evolution occurred. A Dry Ice–acetone mixture was used to maintain the reaction temperature at −20°. In this case, ethanol was not circulated through the quartz jacket. Instead, that area of the jacket through which coolant would normally flow was filled with ethanol. The photolyzed solution exhibited no optical activity at the sodium D line and its ORD spectrum gave no indication of significant activity in the range 450–290 mμ.

A portion (25 ml) of the photolyzed solution was analyzed by preparative glpc at 285°. An analytical run indicated the presence of three components with retention times of 1.5, 1.9, and 10 min, respectively. The two components with the shortest retention times were collected with the solvent and the major component with the longest retention time was a slightly yellow solid, 0.98 g (65.3% based on the fraction analyzed). Two recrystallizations of this material from methanol gave a colorless, crystalline solid, mp 100–133°. Solutions of this compound exhibited no optical activity at the sodium D line (*c* 3.758, 2,2,2-trifluoroethanol) or in the region of 450–200 mμ (ORD, *c* 0.6484, 2,2,2-trifluoroethanol).[28] The broad melting point range indicated that the compound was a mixture of two isomers of coupled diester, and the corresponding infrared and nmr data were essentially identical with those of LMDE and HMDE.

Tetrahydrofuran was removed by rotary evaporation (40°) from the remaining photolyzed solution (75 ml), and, after distillation of the photolysis mixture at 80° (0.25 mm), a mixture of colorless solid and a minimum of yellow liquid remained. The

(28) The coupled products exhibited no optical activity at the sodium D line or in the indicated ORD range prior to their purification by recrystallization.

(29) The overall yields summarized in Table I were calculated on the basis of the fact that the original photolysis mixture weighed 15.3 g and that, after nearly complete separation of the coupled products, a 4-g portion of the remaining mixture which weighed 12.4 g was analyzed by column chromatography.

ORD spectrum of the distilled liquid products (c 2.500, methanol) showed no optical activity in the range 300–208 mμ. The residue was washed with 50 ml of ether and subsequent filtration gave 3.1 g (67.4% based on the fraction distilled) of colorless solid. Two recrystallizations of this compound from methanol afforded a colorless, crystalline solid, mp 100–133°, whose infrared and nmr spectra were identical with those of the material obtained by preparative glpc. Samples of the compound (c 3.216, 2,2,2-trifluoroethanol) and of the ether filtrate failed to exhibit optical activity at the sodium D line and in the 450–200-mμ range (ORD) (c 0.6132, 2,2,2-trifluoroethanol):[28] ν_{max}^{Nujol} 2240 (C≡N) and 1740 cm^{-1} (C=O); nmr (internal standard DSS, DMSO-d_6) τ 8.58 (singlet, 6 H, CCH_3), 7.95 (multiplet, 4 H, $CH_2CH_2COOCH_3$), 7.45 (multiplet, 4 H, $CH_2CH_2COOCH_3$), and 6.38 (singlet, 6 H, $COOCH_3$).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.07; H, 7.12; N, 10.01.

Photochemical Decomposition of (+)-Dimethyl 4,4′-Azobis(4-cyanopentanoate) at −50°.—A solution of 7.3 g (23.7 mmol) of (+)-dimethyl 4,4′-azobis(4-cyanopentanoate), $[\alpha]^{25}D$ +51.0°, in 100 ml of tetrahydrofuran (freshly distilled from $LiAlH_4$) was irradiated in the usual manner. A Dry Ice–acetone mixture was used to maintain the reaction temperature at −50°, and in this case ethanol was circulated through the quartz jacket. Quantitative nitrogen evolution occurred after intermittent irradiation for 46 hr. The photolyzed solution exhibited no significant optical activity in the range of 450–290 mμ (ORD).

Distillation of the photolysis mixture, employing the conditions described in the preceding experiment, ultimately gave 4.5 g (68% yield) of coupled products. Two recrystallizations of this isomeric mixture from methanol afforded a colorless, crystalline solid, mp 100–133°, whose infrared and nmr spectra were identical with those of the mixture obtained in the preceding experiment. Samples of this mixture exhibited no optical activity at the sodium D line (c 3.518, 2,2,2-trifluoroethanol) and in the range of 450–200 mμ (ORD) (c 0.5984, 2,2,2-trifluoroethanol).[28] An ORD spectrum of the distilled products (c 2.430, methanol) failed to show any activity in the range of 300–208 mμ.

Vacuum Sublimation of the Mixture of LMDE and HMDE.—A sample of the isomeric mixture of coupled diesters (1.5 g) was sublimed at 50° (0.025 mm) for 48 hr, after which time 0.68 g of colorless solid, mp 103–120°, was collected. This material was resublimed at 45° (0.025 mm) for 24 hr to give 0.51 g of solid, mp 104.5–118°. The melting point range could not be significantly altered (mp 105–117.5°) after a third sublimation at 40° (0.025 mm). Recrystallization of the latter sublimate and residue afforded a colorless, crystalline solid, mp 105.5–114°. A second recrystallization from methanol failed to narrow the melting-point range.

The residue from the first sublimation, 0.78 g, mp 122–134°, and that from the second, 0.24 g, mp 124–135°, were combined and recrystallized from methanol to give a colorless, crystalline solid, mp 126–137°. Subsequent recrystallization from methanol did not change the melting-point range. The infrared and nmr spectra of both impure isomers were essentially identical with those of the parent mixture and of pure LMDE and HMDE.

Kinetics of the Thermal Decompositions.—The apparatus employed was similar to that used by Overberger and Gainer.[30] It consisted of an inner chamber into which the sample was introduced and an outer chamber in which a suitable liquid was refluxed. A 10-mm-diameter tube allowed the nitrogen evolved to pass from the inner chamber, through a cooling coil at 27°, into a 100-ml gas buret (graduated in 0.1 ml) surrounded by a glass jacket through which water maintained at 27° flowed. The course of each decomposition was followed by measuring the rate of evolution of nitrogen, which displaced a volume of mercury.

For a typical run, 15 ml of N,N-dimethylacetamide was placed in the inner chamber. A suitable liquid, chosen according to the temperature desired (ethanol at *ca.* 100°), was refluxed in the outer chamber. When the temperature had reached equilibrium and the levels of mercury in both sides of the manometer were brought to the same level, the initial volume reading (v_i) from the buret was recorded. The sample (*ca.* 300 mg) was quickly introduced into the inner chamber, which was stoppered with a Reducing-Bushing-type adapter containing a thermometer immersed in the solution of azo compound. Stirring of the solution was effected continuously with a Teflon-coated stirring bar, and no variation in reaction temperature was observed during each of the decompositions. At specific time intervals (based on the rate of nitrogen evolution), the volume of nitrogen evolved (v_t) was recorded. This procedure was followed until *ca.* 75–80% of the theoretical volume of nitrogen had been evolved. When the evolution of nitrogen ceased, that volume reading was taken as v_t; these final readings agreed well with the stoichiometric values. All v_t readings were recorded after 10–12 half-times had elapsed and v_∞ was determined from the relationship $v_\infty = v_t - v_i$.

Registry No.—(−)-4,4′-Azobis(4-cyanopentanoic acid), 23886-45-5; *meso*-4,4′-azobis(4-cyanopentanoic acid), 23886-46-6; (±)-4,4′-azobis(4-cyanopentanoic acid), 23886-47-7; (+)-4,4′-azobis(4-cyanopentanoic acid), 23942-62-3; (+)-4,4′-azobis(4-cyanopentanoic acid) (quinine salt), 23886-48-8; (−)-dimethyl 4,4′-azobis(4-cyanopentanoate), 23886-49-9; *meso*-dimethyl 4,4′-azobis(4-cyanopentanoate), 23886-50-2; (+)-dimethyl 4,4′-azobis(4-cyanopentanoate), 23886-51-3; dimethyl 4,5-dicyano-4,5-dimethyloctane-1,8-dioate, 23886-55-7; 4,5-dicyano-4,5-dimethyloctan-1,8-oic acid, 23886-56-8; **2**, 23886-52-4; **3**, 23886-53-5; **4**, 23886-54-6.

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(30) C. G. Overberger and H. Gainer, *J. Amer. Chem. Soc.*, **80**, 4561 (1958).

Vacuum Pyrolysis of Nitrostyrenes

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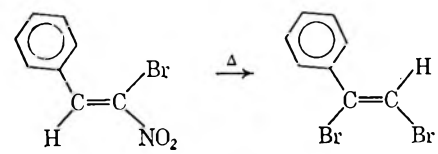
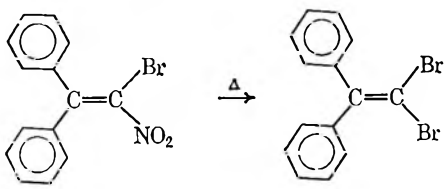
The gas-phase vacuum pyrolysis of a series of nitrostyrenes produced major products which are the result of intramolecular nonradical reactions, in contrast to the known behavior of alkylnitro compounds and nitroaromatic compounds. β-Methyl-β-nitrostyrene, for instance, yields benzaldehyde, acetonitrile, and methyl isocyanate as major products. Mechanisms for the major products are proposed and comparisons with mass spectral and photochemical processes are made and discussed.

The pyrolytic behavior of nitroalkanes[1b] has recently been reviewed, and that of nitroaromatics[2] has been the subject of much current interest. In both instances the main pyrolysis reaction involves cleavage of the nitro group to generate two radicals which lead to the observed products. Similarities in the mass spectral behavior of nitroaromatics[3] and nitrostyrenes[4] coupled with the known photochemical lability of nitro olefins[5,6] suggested that nitrostyrenes might exhibit thermal reactions analogous to those observed for nitroaromatics.

Two reports on the pyrolysis of nitrostyrenes have been published.[7,8] The pyrolysis of β-bromo-β-nitrostyrenes[7] reportedly yields α,β- or β,β-dibromostyrenes (eq 1 and 2) *via* the divalent carbon intermediate **1**,

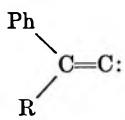


(1)



(2)

which adds bromine. The α,β-dibromo product (eq 1) was postulated to arise by a 1,2-hydrogen migration. A



1, R = H, C_6H_5

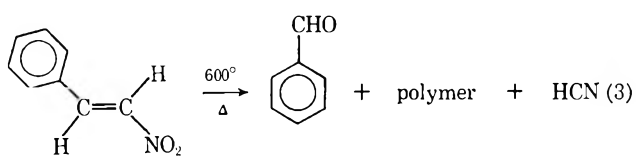
subsequent study on the pyrolysis of simple nitrostyrenes in the heated inlet (230°) of a mass spectrometer,[8] with product identification from the mass spectrum, revealed nitrostyrenes to be quite thermally stable. The only pyrolysis reaction observed was the elimination of HNO_2 from β-nitrostyrene itself.

Our observations of pronounced thermal effects on the mass spectra of nitrostyrenes prompted us to examine in more detail their thermal chemistry under conditions of high temperature and low pressure. The results are described below. Vapor phase chromatography, nuclear magnetic resonance, infrared and mass spectral techniques, along with authentic compound comparisons, were used to prove structures of products. Details, including a description of the apparatus used, are given in the Experimental Section.

Results and Discussion

The pyrolysis experiments were generally conducted at pressures in the range of 0.001–0.005 mm, but occasionally higher pressures were employed. The nitrostyrenes were found to be thermally quite stable and did not decompose at temperatures less than 400°, while even at 500° the pyrolysis reactions were often incomplete. At temperatures equal to or in excess of 600°, pyrolysis was complete. Generally 0.1–0.4 g of material was pyrolyzed during an 8–12-hr period. The yield of products was 60–70%, with the remainder being gaseous or carbonaceous materials.

Pyrolysis of β-nitrostyrene (**2**) at 600° resulted in the formation of benzaldehyde, a white, polymeric material, and a gas, probably hydrogen cyanide, as indicated in eq 3. The polymeric material changed to a red-brown



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color upon prolonged exposure to air, and could not be recrystallized from any of a variety of solvents. The pyrolysis of 1,1-diphenyl-2-nitroethylene (**3**) under similar conditions gave benzophenone, the same polymeric material, and probably hydrogen cyanide. The formation of the same polymeric material from **2** and **3** implicated the β-carbon atom for its formation. It was postulated that placing an alkyl group on the β-carbon atom might lead to more stable pyrolysis products.

Indeed, this was borne out by the absence of any polymeric products in the pyrolysis of β-methyl-β-nitrostyrene (**4**), which yielded acetonitrile, benzaldehyde, benzene, methyl isocyanate, methyl phenyl-

(1) (a) HEW Predoctoral Fellow, 1966–1969; (b) G. M. Nazin, G. B. Manelis, and F. I. Dubovitskii, *Usp. Khim.*, **37**, 1443 (1968).

(2) (a) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 724 (1967); (b) E. K. Fields and S. Meyerson, *ibid.*, **89**, 3224 (1968); (c) E. K. Fields and S. Meyerson, *J. Org. Chem.*, **34**, 3114 (1967); (d) E. K. Fields and S. Meyerson, *Tetrahedron Lett.*, 1201 (1968).

(3) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 512.

(4) T. H. Kinstle and J. G. Stam, *Org. Mass Spectrom.*, in press.

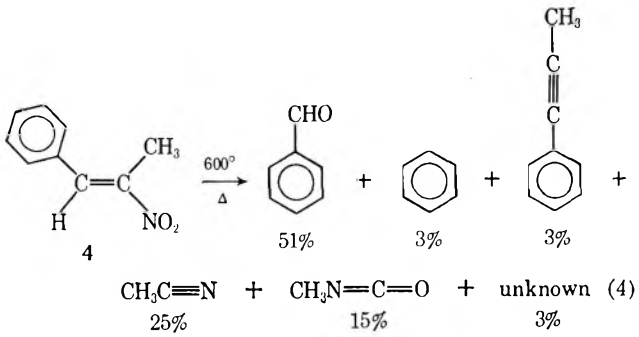
(5) O. L. Chapman, P. G. Cleveland, and E. D. Hoganson, *Chem. Commun.*, 101 (1966).

(6) O. L. Chapman, D. C. Heckert, J. W. Reasoner, and S. P. Thackaberry, *J. Amer. Chem. Soc.*, **88**, 5550 (1966).

(7) C. F. H. Allen and C. V. Wilson, *J. Org. Chem.*, **5**, 146 (1940).

(8) C. F. H. Allen and G. P. Happ, *Can. J. Chem.*, **42**, 650 (1964).

acetylene, and an unidentified material (less than 3.5% of total products) as indicated in eq 4. If the head

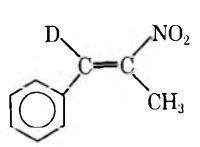


temperature was increased above that indicated in the Experimental Section, additional unidentified products were formed, probably by intermolecular reactions. The pyrolysis of 1-(α-naphthyl)-2-nitropropene (**5**) and 1,1-diphenyl-2-nitropropene (**6**) under similar conditions gave products analogous to those described above for pyrolysis of **4**.

The formation of methylphenylacetylene (3%) among the pyrolysis products from β-methyl-β-nitrostyrene (**4**) can be explained as the elimination of nitrous acid. The formation of methyl-α-naphthylacetylene in the pyrolysis of **5** must occur in a similar manner. Apparently, β-nitrostyrene (**2**) does not decompose in this manner, since no phenylacetylene was detected among the pyrolysis products. Cleavage of the nitro group to give a vinyl radical with the subsequent loss of hydrogen is reminiscent of the pyrolytic behavior of nitroaliphatics[1b] and nitroaromatics,[2] but it constitutes only a minor decomposition pathway for nitrostyrenes.

The formation of benzene (3%) in the pyrolysis of β-methyl-β-nitrostyrene (**4**) can be explained in terms of a very similar mechanism. Instead of eliminating a nitro group and a hydrogen atom to give methylphenylacetylene, elimination of the nitro group can be followed by loss of a phenyl radical with the concurrent or subsequent abstraction of a hydrogen atom from another organic molecule. As is usual in such reactions, some tarry material is formed. No propyne is observed among the pyrolysis products of **4**. A similar reaction sequence can be envisioned for the formation of benzene and naphthalene in other pyrolysis reactions. The absence of benzene formation in the pyrolysis of β-nitrostyrene (**2**) and the formation of benzene in the pyrolysis of 1,1-diphenyl-2-nitropropene (**6**) demonstrate that benzene is not being formed by decarboxylation of benzaldehyde. Furthermore, benzaldehyde is not converted into benzene under the pyrolysis conditions.

The specifically deuterated compound **9** was pyrolyzed and the benzene which was formed contained no deuterium atom. This is further evidence against the



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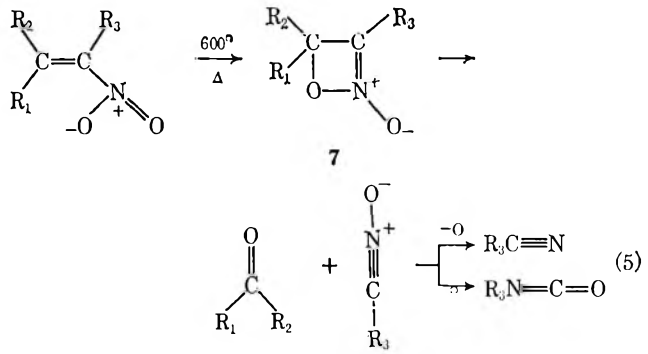
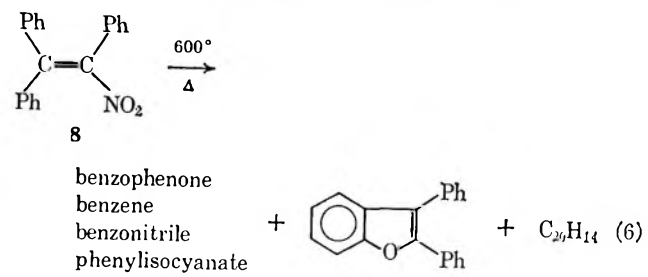
benzaldehyde decarboxylation route to benzene and is strong evidence for hydrogen abstraction occurring from the β-methyl group of either **9** or the propyne obtained by elimination from **9**.

The isolation of carbonyl compounds as major products in the pyrolysis of **2**–**6** suggests that one of the oxygen atoms of the nitro group is acting as a nucleophile in an addition to the α-carbon atom of the nitrostyrenes, as depicted in generalized eq 5. In agreement



with this proposal is the well-known propensity of nitroolefins to undergo addition reactions with a variety of nucleophiles.[9] The subsequent decomposition of the cyclic structure **7** formed in this way would give carbonyl compounds and nitrile oxides. Since nitrile oxides are known to rearrange thermally to isocyanates,[10] the origin of these products is easily explained. The nitriles observed as products in the pyrolysis reactions are probably formed by the thermal loss of oxygen from the nitrile oxides. Although this is not a known thermal reaction of nitrile oxides, chemical removal of oxygen is known to occur easily.[11] The polymer formed in the pyrolysis of β-nitrostyrene (**2**) and 1,1-diphenyl-2-nitroethylene (**3**) can be plausibly accounted for, since HNCO is known to polymerize spontaneously.[12] Also in accord with this mechanism is the fact that compound **9** gives only benzaldehyde-d_1 with all the label at the carbonyl carbon.

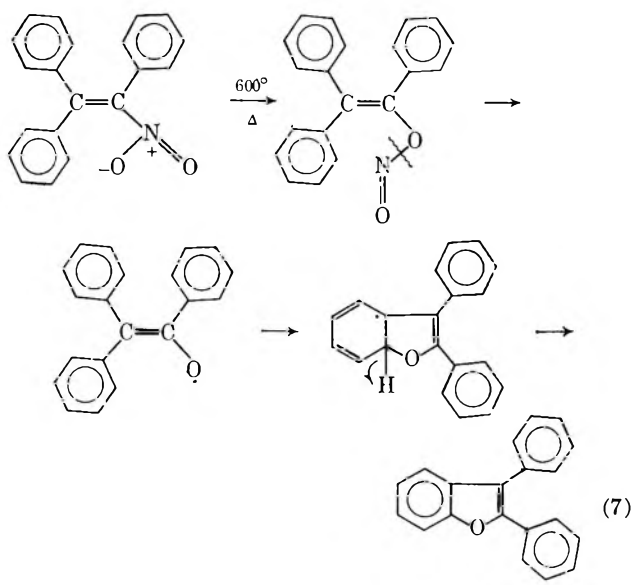
The effect of substituting a phenyl ring on the β-carbon atom was investigated by pyrolyzing nitrotriphenylethylene (**8**). Identified were the expected products benzene, benzophenone, benzonitrile, and phenyl isocyanate, undoubtedly formed by reactions whose mechanisms have been discussed above, as well the additional compounds 2,3-dibenzofuran and a $C_{20}H_{14}$ hydrocarbon of unproved structure (eq 6). The



initial step in the formation of the $C_{20}H_{14}$ hydrocarbon is probably loss of the nitro group to form a vinyl radical. The vinyl radical can then rearrange with expulsion of a hydrogen atom to give the product, which is possibly 9-phenylphenanthrene.

(9) V. V. Perekalin, "Unsaturated Nitro Compounds," Daniel Davey and Co., Inc., New York, N. Y., 1964.
(10) C. Grundman and S. K. Datta, *J. Org. Chem.*, **34**, 2016 (1969).
(11) C. Grundman, *Fortsch. Chem. Forsch.*, **7**, 62 (1966).
(12) E. E. Turner and M. M. Harris, "Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1952, p 117.

The formation of 2,3-diphenylbenzofuran from **8** results from a new type of decomposition. The first step must be a thermally induced nitro–nitrite rearrangement. A similar rearrangement has been proposed to explain some of the products from the thermal decomposition of nitrobenzene.[2b] The formation of a radical by breaking the nitrogen–oxygen bond of the nitrite is followed by attack on a phenyl ring with expulsion of a hydrogen atom to give 2,3-diphenylbenzofuran, as indicated in eq 7.



(7)

These pyrolysis results from nitrostyrenes are quite different from those observed for nitroalkanes[1] and nitroaromatics, where only radical reactions are of importance. With nitrostyrenes, intramolecular reactions involving the double bond are of primary importance while radical reactions are of only secondary importance. Likewise, upon electron impact, nitrostyrenes[4] also exhibit important fragmentations involving the double bond.

There appear to be a number of correlations between the mass spectral fragmentations of nitrostyrenes and their thermal decomposition, for example, the observation of carbonyl and acetylenic ions. However, these ions are generally of low abundance in the absence of thermal effects. The nitro–nitrite rearrangement observed in the pyrolysis of nitrotriphenylethylene (**8**) is also observed in the mass spectrum of **8**.

The synthetic utility of the pyrolysis reaction is of limited value because of the variety of products obtained. However, it could be useful to obtain small quantities of unusual nitriles and isocyanates. We are presently exploring the scope and limitations of these interesting pyrolysis reactions.

Experimental Section

Description of Pyrolysis Apparatus.—All pyrolysis experiments were performed using a pyrolysis tube (12 × 1 in.) made from Vycor glass and filled with Vycor chips. The pyrolysis tube was heated with a Sola Basic Industries Lindberg Hevi-Duty Model 55035-A tube furnace, and the pyrolysis temperatures reported are those recorded by a Platinel II thermocouple. The temperature read is that between the pyrolysis tube and the heating element; thus the actual temperature inside the pyrolysis tube is probably slightly lower. The vacuum for the pyrolysis apparatus was created by a Consolidated Vacuum Corp. Type VMF oil diffusion pump backed by a Welch Duo-Seal vacuum pump. The samples were sublimed into the pyrolysis tube from an aluminum oven fitted with a buried thermometer and heated with a Glas-Col heating tape. Pyrolysis products were trapped in a U-tube cooled in liquid nitrogen.

β-Nitrostyrene (**2**).—The procedure of Worral[13] was used to prepare β-nitrostyrene (**3**), mp 55–56° (lit.[13] mp 57–58°).

β-Methyl-β-nitrostyrene (**4**).—An adaptation of Heinzelman's[14] procedure was used to prepare **4** by *n*-butylamine-catalyzed condensation of benzaldehyde and nitroethane in toluene using a Dean–Stark apparatus to remove water, mp 64° (lit.[15] mp 65°).

1-(α-Naphthyl)-2-nitropropene (**5**).—The desired compound was prepared by a modification of the method of McCarthy and Kahl.[16] A solution of 31.2 g of 1-naphthaldehyde (Aldrich), 15.0 g of nitroethane, 1 ml of butylamine, and 20 ml of absolute ethyl alcohol was kept in the dark at room temperature for 2 weeks. The red bottom layer was separated and concentrated to a red oil at reduced pressure. Dissolution of the oil in ethyl alcohol and cooling gave dark brown crystals. Charcoal decolorization and several recrystallizations from ethanol gave 28.7 g of light yellow needles: mp 65–67°; ir (CCl_4) 6.02 (C=C), 6.6 (NO_2), and 7.55 μ (NO_2); nmr (CCl_4) δ 2.3 (d, 3, CH_3), 7.3–7.9 (m, 7), and 8.5 (s, 1, *peri* H).

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 72.90; H, 5.21; N, 6.58. Found: C, 72.88; H, 5.30; N, 6.64.

1,1-Diphenyl-2-nitroethylene (**3**).—This compound was prepared from 1,1-diphenylethylene according to the procedure of Govindachari, Pai, and Rao.[17] Light yellow needles were obtained after recrystallization, mp 86.5° (lit.[17] mp 87°).

1,1-Diphenyl-2-nitropropene (**6**).—The desired compound was prepared from 1,1-diphenylpropene using the procedure for **3**.[17] The oil resulting from decomposition of 5.1 g of nitrosite was vacuum distilled at 139–142° (1 mm) to give 1.85 g of thick yellow oil which was dissolved in ethanol and cooled in an acetone–Dry Ice bath to yield light yellow crystals: mp 49–50°; ir (CCl_4) 6.01 (C=C), 6.60 (NO_2), and 7.4 μ (NO_2); nmr (CCl_4) δ 2.3 (s, CH_3) and 7.0–7.4 (m, C_6H_5).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.32; H, 5.44; N, 5.86. Found: C, 75.39; H, 5.47; N, 5.79.

Nitrotriphenylethylene (**8**).—This compound was prepared from triphenylethylene according to the procedure of Govindachari, Pai, and Rao.[17] The product obtained by decomposition of the nitrosite was recrystallized from ethanol to give light yellow needles, mp 176–177° (lit.[17] mp 178°).

α-Deuterio-β-methyl-β-nitrostyrene (**9**).—The method of Wiberg[18] was used to prepare 1.25 g of α-deuteriobenzaldehyde, which was condensed with 1.5 g of nitroethane using the procedure of Heinzelman[14] to yield 0.97 g of **9**: mp 63.5–64°; ir (CCl_4) 6.02 (C=C), 6.57 (NO_2), and 7.55 μ (NO_2). Low-voltage mass spectrometry indicated the following deuterium incorporation: 1.2% d_0, 98.8% d_1.

2,3-Diphenylbenzofuran.—This compound was prepared according to the procedure of Wacek and Daubner.[19] The product was purified by elution from a silica gel (Baker) chromatography column using petroleum ether. Evaporation of petroleum ether at reduced pressure gave light white crystals, mp 123–124° (lit.[19] mp 122–124°).

Pyrolysis of β-Nitrostyrene (**2**).—Pyrolysis of β-nitrostyrene (**7**) at 400° (0.001 mm)[20] with a head temperature of 50–52° resulted in the recovery of only starting material, as shown by nmr. The pyrolysate of **2** at 600° (0.005 mm) with a head temperature of 50–55° was washed from the cold trap with several milliliters of carbon tetrachloride. This solution became warm and then hot as white, amorphous precipitate formed. The precipitate isolated by filtration exhibited spectral characteristics of a polymer and turned dark red upon prolonged exposure to air. Nmr analysis of the filtrate revealed the presence of benzaldehyde: nmr (CCl_4) δ 7.2–7.8 (m, 5, C_6H_5) and 9.92 (s, 1, HCO).

(13) D. E. Worral, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N.Y. 1932, p 413.
(14) R. V. Heinzelman, ref 13, Coll. Vol. IV, 1963, p 573.
(15) H. Hass, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).
(16) W. C. McCarthy and R. J. Kahl, *ibid.*, **21**, 1118 (1956).
(17) T. R. Govindachari, B. R. Pai, and U. R. Rao, *Proc. Indian Acad. Sci., Sect. A*, **48**, 111 (1958).
(18) K. B. Wiberg, *J. Amer. Chem. Soc.*, **76**, 5371 (1954).
(19) A. Wacek and H. Daubner, *Monatsh. Chem.*, **81**, 246 (1951).
(20) These pressure measurements were taken on the pump side of the pyrolysis column. Although the pressures at the point of pyrolysis were undoubtedly somewhat higher, the sublimination rate was held very low in order to minimize the pressure increase.

Pyrolysis of 1,1-Diphenyl-2-nitroethylene (3).—The pyrolysis of 1,1-diphenyl-2-nitroethylene (**3**) was effected at 600° (0.001 mm) with a head temperature of 75–78°. The pyrolysate was washed from the cold trap with carbon tetrachloride and gave the same white precipitate observed for **2**. Nmr analysis of the filtrate revealed the presence of benzophenone: nmr (CCl_4) δ 7.2–7.8 (m, C_6H_5). The pyrolysate obtained from the pyrolysis of **3** at 700° (0.002 mm) with a head temperature of 78–80° was identical with that obtained at 600°.

Pyrolysis of β-Methyl-β-nitrostyrene (4).—The pyrolysis of β-methyl-β-nitrostyrene was effected at 600° (0.001 mm) with a head temperature of 50–55°. Analysis of the pyrolysate by vpc indicated the presence of at least six components and the following peaks were observed in the mass spectrum (70 eV): *m/e* 106, 105, 78, 77, 76, 57, 52, 51, 50, 41, 40, and 39. The pyrolysate was shown to consist of acetonitrile, benzaldehyde, benzene, methyl isocyanate, and methylphenylacetylene by comparison of vpc retention times and spectral data with those of authentic samples. The following were recorded for the pyrolysate: ir (CCl_4) 4.25–4.55 (broad band) and 5.85 μ (CO); nmr(CCl_4) δ 1.9 (s, CH_3CN), 2.02 (s, $C_6H_5CCCH_3$), 2.1 (s, unknown), 3.0 (s, CH_3NCO), 7.15–7.3 (m, $C_6H_5CCCH_3$), 7.27 (s, C_6H_6), 7.4–7.8 (m, C_6H_5CHO), and 9.92 (s, C_6H_5CHO). A sixth minor product was not identified. The product ratios were determined by nmr. The pyrolysis of **4** at 500° (0.250 mm) with a head temperature of 60–70° was shown to give starting material and the aforementioned products by nmr analysis. Pyrolysis of **4** at 400° (0.100 mm) with a head temperature of 65–70° returned starting material only.

Pyrolysis of 1-(α-Naphthyl)-2-nitropropene (5).—The pyrolysis of 1-(α-naphthyl)-2-nitropropene (**5**) was accomplished at 600° (0.001 mm) with a head temperature of 52–53°. Nmr analysis of the pyrolysate indicated the presence of acetonitrile, methyl isocyanate, and naphthaldehyde. Vpc analysis of the pyrolysate (BDS, 175°) established the presence of naphthalene. Vpc data also suggested the presence of methyl-α-naphthylacetylene, which was confirmed by an ir absorption at 4.5 μ (C≡C) in the absence of acetonitrile and methyl isocyanate. A minor component of the pyrolysate was not identified. The following nmr data were obtained for the pyrolysate: nmr (CCl_4) δ 1.9 (s, CH_3CN), 2.15 (s, $C_{10}H_7CCCH_3$), 2.2 (s, unknown), 7.2–8.2 (m, $C_{10}H_7CHO$ and $C_{10}H_8$), and 10.33 (s, $C_{10}H_7CHO$).

Pyrolysis of 1,1-Diphenyl-2-nitropropene (6).—Pyrolysis of 1,1-diphenyl-2-nitropropene (**6**) was carried out at 700° (0.001 mm) with a head temperature of 50–51°. Nmr and vpc analyses of the pyrolysate indicated the presence of acetonitrile, benzene, benzophenone, methyl isocyanate, and an unidentified product: nmr (CCl_4) δ 1.9 (s, CH_3CN), 2.1 (s, unknown), 3.0 (s, CH_3NCO), 7.28 (s, C_6H_6), and 7.2–7.9 [m, $(C_6H_5)_2CO$].

Pyrolysis of Nitrotriphenylethylene (8).—Pyrolysis of nitrotriphenylethylene was accomplished at 600° (0.001 mm) with a head temperature of 101–105°. Vpc analysis of the pyrolysate demonstrated the presence of benzene, benzonitrile, benzophenone, and phenyl isocyanate. The presence of benzonitrile, phenyl isocyanate, and benzophenone was further confirmed by ir data: ir (CCl_4) 4.35–4.60 (nitrile–isocyanate) and 6.02 μ (CO). A considerable portion of the pyrolysate solidified before reaching the cold trap. Analysis of this material by mass spectrometry revealed the presence of 2,3-diphenylbenzofuran (*m/e* 270) and a $C_{20}H_{24}$ hydrocarbon (*m/e* 254).

Registry No.—**2**, 102-96-5; **3**, 5670-69-9; **4**, 705-60-2; **5**, 23854-03-7; **6**, 15795-69-4; **8**, 5670-70-2.

Acknowledgment.—The authors gratefully acknowledge the financial support supplied by grants from Eli Lilly & Co. and the Petroleum Research Fund administered by the American Chemical Society.

Photochemical Oxidations. III. Photochemical and Thermal Behavior of α-Hydroperoxytetrahydrofuran and Its Implications Concerning the Mechanism of Photooxidation of Ethers[1a]

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Received July 7, 1969

The suspected intermediate peroxide in the photooxidation reaction of tetrahydrofuran (THF) was synthesized, and its thermal and photochemical behavior was studied. Liquid-phase thermal decomposition of a dilute peroxide solution gives rise to α-hydroxytetrahydrofuran, whereas vpc decomposition produces α-hydroxytetrahydrofuran and butyrolactone. Photochemically, the peroxide yields only α-hydroxytetrahydrofuran and the rate of production follows first-order kinetics. Using ir analysis and iodimetry, the rates of formation of the products in the photooxidation of THF were determined, and a modified mechanism was proposed for this reaction.

In previous papers of this series it was postulated that the photooxidation of ethers proceeds through the α-hydroperoxides of ethers.[2,3] In order to obtain further experimental data on the role of peroxides in these reactions, the thermal and photochemical behavior of α-hydroperoxytetrahydrofuran (I) has been studied. It was hoped that the hydroperoxide of diethyl ether could also be studied, but this was not possible, since the compound is too unstable to be prepared. In our previous work,[3] the rate of accumulation for the two products formed in the photooxidation of tetrahydrofuran (THF), *i.e.*, butyrolactone (II) and α-hydroxytetrahydrofuran (III), had been followed by vpc. However, since peroxides were also found in the reaction mixture, there was the possibility that thermal decomposition of these peroxides may have occurred during the vpc analysis and given rise to a portion of the products found. Therefore, it was necessary that the thermal decomposition of α-hydroperoxytetrahydrofuran, the postulated peroxide, be studied.

Compound I was prepared and a solution of it in THF was injected into a gas chromatograph with the injection chamber at 100°. It was found that both II and III were produced under these conditions. Also no trace of I could be detected in the vpc spectrum. The molar ratio of products obtained (II to III) was *ca.* 3:1, with the exact ratio depending on the experimental conditions and techniques. Therefore, it is obvious that the vpc results for rates of product accumulation during the photooxidation contain an

(1) (a) Presented at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969; (b) Taken in part from the Ph.D. thesis of C. T. Wang, University of North Dakota, June 1969.

(2) V. I. Stenberg, R. D. Olson, C. T. Wang, and N. Kulevsky, *J. Org. Chem.*, **32**, 3227 (1967).

(3) N. Kulevsky, C. T. Wang, and V. I. Stenberg, *ibid.*, **34**, 1345 (1969).

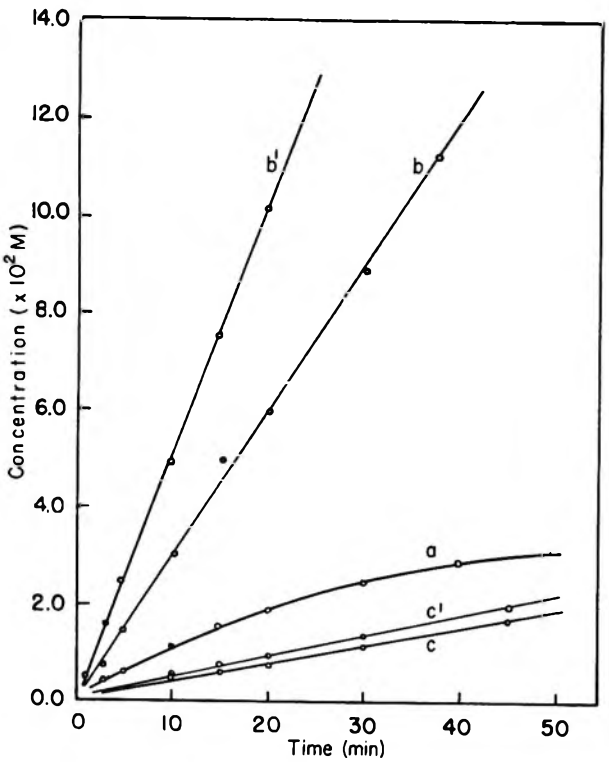


Figure 1.—Rates of product formation during photooxidation of tetrahydrofuran: (a) α-hydroperoxytetrahydrofuran; (b) α-hydroxytetrahydrofuran; (c) butyrolactone; (b′ and c′) α-hydroxytetrahydrofuran and butyrolactone, respectively, in the same process with the addition of 9.14×10^{-2} *M* α-hydroperoxytetrahydrofuran prior to the start of the irradiation.

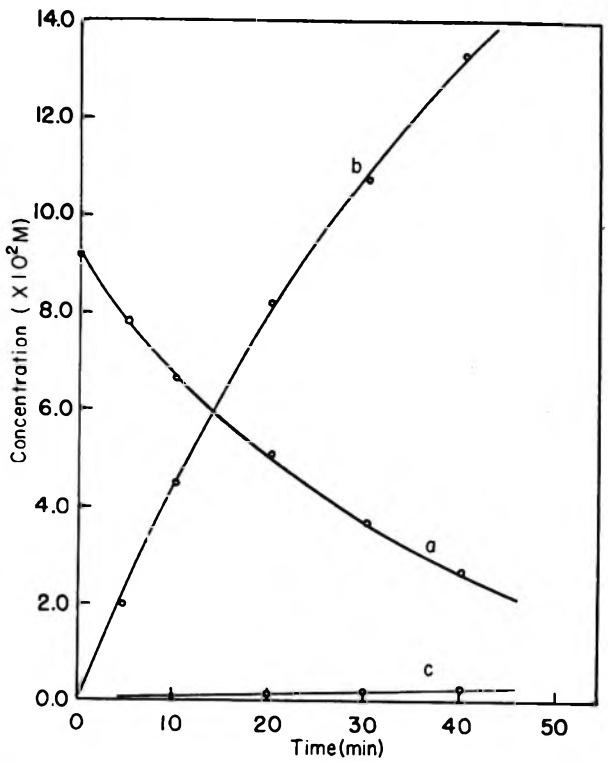


Figure 2.—Plots of the concentrations of (a) α-hydroperoxytetrahydrofuran, (b) α-hydroxytetrahydrofuran, and (c) butyrolactone *vs.* time for the photodecomposition of β-hydroperoxytetrahydrofuran.

inherent error which is proportional to the amount of hydroperoxide present.

There remained the possibility that the thermal decomposition of I in solution could play a significant role in the photooxidation of THF. As a consequence, the thermal decomposition of a THF solution of I in a sealed tube at 100° was studied. As opposed to the vpc results, only III is produced. At room temperature or lower the thermal reaction of I is very slow and, for the time period of the irradiation, it is not likely to be the source of III in the photooxidation of THF, since this reaction is also run at low temperatures. Furthermore, the pyrolysis of I in the injection chamber or column of the vpc is more complex than the liquid-phase pyrolysis. Apparently, the decomposition in the chamber may occur wholly in the vapor state or in a combination of liquid and vapor states, and this probably accounts for the variable ratio of products in the vpc work.

To obtain more accurate rates of product-accumulation data for the photochemical oxidation of THF, an analytical method which would not decompose the hydroperoxide in the reaction mixture was necessary. Accordingly, infrared spectrometry was utilized to follow concentrations of the products, II and III, directly on the reaction mixture, while iodimetric titrations were used for the peroxide I. The rates of product accumulation obtained in this way are shown in Figure 1. These demonstrate that even for very short irradiation times all products I–III are formed, III is formed at a faster rate than II, and the hydroperoxide I attains what appears to be a steady-state concentration on prolonged irradiation.

With the data described above, it still was not possible to determine if the peroxide in the reaction solution, presumably the hydroperoxide I, serves as a precursor of II and III or if II and/or III are generated by an independent pathway. With this question in mind, a study of the photochemical behavior of the peroxide I in THF was done at about the concentration it has in the photooxidation reactions. In these experiments, the peroxide I degrades rapidly in a nitrogen atmosphere upon irradiation (Figure 2), yielding one major product, the hydroxy ether III, with only a trace of the lactone II (see Figure 2). A further observation is that *ca.* 2 mol of III are formed from every mole of I decomposed. The kinetics of the reaction are first order with respect to the peroxide concentration, as shown in Figure 3. It is noteworthy that this reaction is the best and neatest method of preparing III.

From the above data the decomposition of I in THF solution is most likely to be a bimolecular reaction of I with THF. Since THF is present in excess as a solvent whose concentration will not change very much during the course of the reaction, it may be regarded as a constant, and the reaction will be pseudo first order. Furthermore, the data implies that chain processes are not involved in the initial stages of the reaction, possibly owing to the low concentration of reactants. Also it is clear that the lactone II formed in the photooxidation of THF is not formed directly from the peroxide. Presumably the association of I with THF *via* hydrogen bonding results in a bimolecular photodecomposition.

There remained the possibility that I in the presence of oxygen may photochemically yield II. However, when a dilute THF solution of I is irradiated under oxygen, the evidence does not support this possibility. The data shown in Figure 1 as curve c′ indicate that

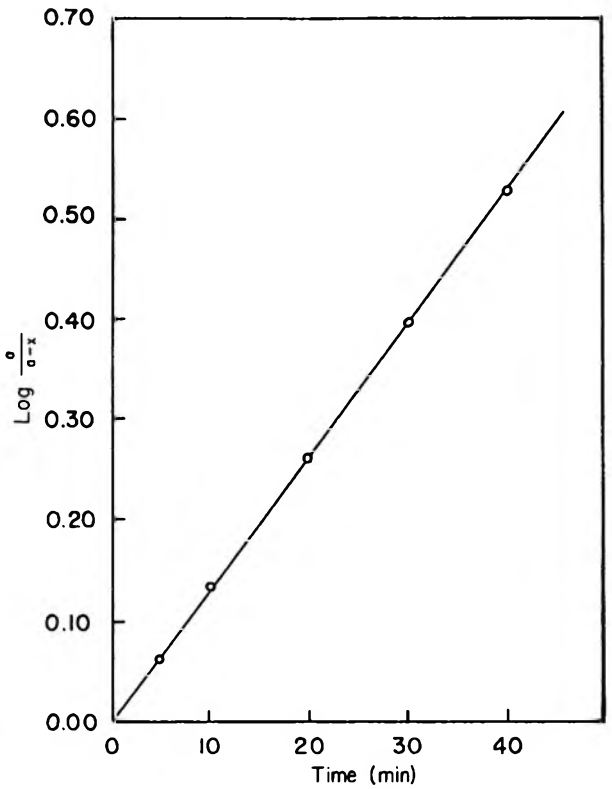


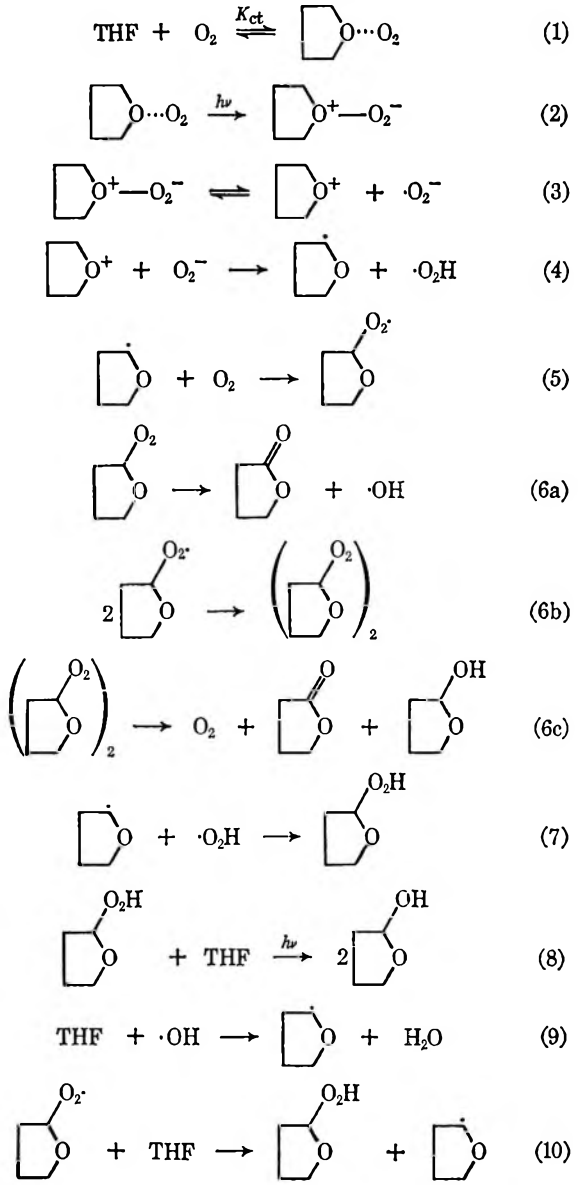
Figure 3.—First-order plot of the photodecomposition of α-hydroperoxytetrahydrofuran.

the rate of formation of II is only slightly faster than without the added peroxide, whereas the rate of formation of III (curve b′) is considerably increased. Thus the observed results can be accounted for simply by an addition of the photooxidation of tetrahydrofuran and the photochemical conversion of the hydroperoxide.

With the data presented above and that presented in previous papers,[1-3] a more detailed mechanism can now be presented for the photooxidation of ethers (Scheme I). Step 1 is the formation of the charge-transfer complex and step 2 is the excitation of this complex by the light, for which the evidence was given in the previous paper. Step 3, a new feature of the mechanism, is the dissociation of the excited-state complex, which is analogous to that proposed for other complexes.[4] For those cases, esr evidence for radical formation was taken as proof of the dissociation. Previously we had suggested that the excited state of the charge-transfer complex underwent a proton shift and then gave the hydroperoxide directly.[3] However, it is now necessary to postulate this dissociation (step 3), since the work presented here demonstrates that the hydroperoxide is not the precursor of the lactone. Steps 4–6a are then postulated as the route for the generation of lactone without going through the hydroperoxide. Step 6a is analogous to one suggested to occur in the oxidation of cyclohexane.[5] Steps 6b and 6c also lead to the formation of the lactone.[4] However, step 6b is not very likely under the conditions of these reactions (solution in THF and low concentration of radicals), as combination of peroxy radicals would be precluded by the ability of THF to trap free radicals. Steps 4, 7, and 10 produce hydroperoxide and take into account the

(4) K. U. Ingold, *Accounts Chem. Res.*, **2**, 1 (1969).
(5) R. Guedj and J. Jullien, *Bull. Soc. Chem. Fr.*, 1501 (1964).

SCHEME I



photochemical decomposition of the hydroperoxide shown in this work.

Experimental Section

Materials.—Tetrahydrofuran (Fisher reagent grade) was purified as described previously.[2,3] α-Hydroperoxytetrahydrofuran was prepared by the method of Grosborne and de Roch[6] and was obtained 95.3% pure. The purity was determined by iodimetric titrations.[7]

Determination of Rates.—The apparatus and procedure were essentially the same as described previously[3] except that, instead of gas chromatography, infrared spectrometry was used in the quantitative determination of products. The same process was also repeated with the addition of I prior to the start of the THF photooxidation. The ir spectra of the reaction mixtures with THF as a reference were monitored over the initial 50 min. The path length of the matched ir cells was 0.2 mm. A Beckman Model IR-12 spectrophotometer was used. Quantitative measurements were made by comparing the absorbance of irradiated products with that of a mixture of known concentrations of reactant and products. The bands used to follow the concentration of II and III were 1789 and 1735 cm^{-1}, respectively. The peroxide concentration was determined by iodimetric titration.[7]

(6) P. Grosborne and I. S. de Roch, *ibid.*, 2260 (1967).
(7) C. D. Wagner, R. H. Smith, and E. D. Peters, *Anal. Chem.*, **19**, 976 (1947).

Thermal Decomposition of α-Hydroperoxytetrahydrofuran (I). A. Pyrolysis in the Gas Chromatograph.—A 1-μl sample of a 4.3×10^{-2} *M* solution of I in THF was injected into a Beckman GC-5 gas chromatograph equipped with a flame ionization detector and a 6 ft × 0.125 in. Carbowax column on Chromosorb W. The gas chromatogram showed two major peaks for butyrolactone and α-hydroxytetrahydrofuran in a ratio of *ca.* 1:3.

B. Pyrolysis in a Sealed Tube.—A 5-ml solution of 8.6×10^{-2} *M* I in THF was placed in a glass reaction tube which was connected to a vacuum line. The solution was thoroughly outgassed by conventional freeze–pump–thaw techniques. After a final check for noncondensable gases, the glass reaction tube was isolated by sealing off from the line and then allowed to reach room temperature. The sealed tube was then heated in a furnace at 100° for 30 min. The reaction mixture was analyzed and found to contain III as the only major products.

Photodecomposition of α-Hydroperoxytetrahydrofuran.—A solution of 9.1×10^{-2} *M* I in THF was placed in a 3-ml uv spectrophotometric cell. The irradiation procedure used was identical with that described before[3] except that, instead of bubbling oxygen through the solution, a slow stream of nitrogen was maintained. The products were identified by ir and vpc and the progress of the reaction was followed as described above. For each set of data, five or more experiments were required for the points on the curve for the range of 0 to 65% decomposition of I. The irradiation of I under oxygen was performed and analyzed in a similar manner.

Registry No.—I, 4676-82-8; THF, 109-99-9.

Acknowledgment.—We gratefully acknowledge the research support of the National Science Foundation (Grants GP-5312 and GP-8564) for their financial contributions to this project.

Electronic Effects in Solvolysis Reactions. III. Solvolysis of Allyl-Substituted Cumyl Derivatives[1]

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Received September 11, 1969

Synthetic procedures are described for *p*-γ,γ-dimethylallyl-, *p*-α,α-dimethylallyl-, *p*-3-butenyl-, *m*-allyl, *p*-allyl-, and *p*-γ,γ-dideuterioallylcumyl *p*-nitrobenzoates. The possibility of allylic participation during the solvolysis of these compounds in aqueous mixtures was investigated. Substituent constants (σ^+), skeletal rearrangement studies, and kinetic isotope effect measurements were employed to determine the nature and extent of such participation. These data, coupled with the uniformity of activation parameters and the absence of skeletal isomerizations, suggest that inductive effects by the allylic double bond are the major influence in the solvolytic behavior of these esters.

Much interest and experimental work has centered around the stabilizing influence of cyclopropyl and allyl substituents in solvolytic reactions. Both functional groups provide stabilization for developing carbonium ions and, hence, rate enhancements are frequently observed.[3] As a quantitative measure of the electronic effects of the cyclopropyl substituent in carbonium ion reactions, the substituent constant σ^+ was determined from solvolytic studies of substituted cumyl derivatives.[4-6] These data indicated that the *p*-cyclopropyl group (relative to other alkyl groups) exhibited an abnormally large (negative) σ^+ value and that the ability of the substituent to supply electron density was conformationally dependent.[5] It was considered, therefore, of general interest to prepare a number of allyl-substituted cumyl derivatives in order to assess, in more quantitative terms, the stabilizing influence of *m*- and *p*-allyl substituents on developing carbonium ions.

Results

Substituted cumyl *p*-nitrobenzoates were chosen for this investigation and were synthesized, for the most part, by conventional procedures. All esters gave satisfactory elemental analyses.

Water–acetone mixtures were selected as solvolytic media, and rate constants for solvolysis were determined at several temperatures for each of several solvent compositions. Detailed product studies indicated that *p*-nitrobenzoic acid and substituted cumyl alcohols were the only products produced during solvolysis. Under these reaction conditions, isomerization of the double bond in the allyl substituents into conjugation with aromatic ring could not be detected. Similarly, deuterium labeling in the allyl group indicated that carbon skeletal rearrangement did not occur during solvolysis.

Table I summarizes the solvolytic rate data for the substituted cumyl *p*-nitrobenzoates at various temperatures and solvent compositions. In all cases the kinetic runs were followed to at least 70% completion. Agreement between most runs was ±1%.

The standard substituents methyl, *t*-butyl, hydrogen, and chlorine were used to obtain Hammett ρ values under each set of conditions. Good linear correlations were observed in each case ($r = 0.994$). At 46.4° in 60% aqueous acetone, the reaction constant (using Brown σ^+ values) was found to be −4.55, and in 50% aqueous acetone at the same temperature the ρ value was found to be −4.38. A reaction constant of −4.70 was observed in 50% aqueous acetone at 38.0°. These ρ values were then employed to determine σ^+ values of each allyl and butenyl substituent. These data are tabulated in Table II. Values for several other substituents are included for reference.

Table III lists activation parameters for solvolysis of the allyl-substituted esters. Within experimental error, all of the esters have the same energy of activa-

(1) For part II, see L. B. Jones and S. S. Eng, *Tetrahedron Lett.*, 1431 (1968).

(2) Phillips Petroleum Co. Fellow, 1966–1968.

(3) See, for example, J. D. Roberts, R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, and M. S. Silver, *J. Amer. Chem. Soc.*, **81**, 4390 (1959); J. D. Roberts and K. L. Servis, *ibid.*, **85**, 3773 (1964).

(4) L. B. Jones and V. K. Jones, *Tetrahedron Lett.*, 1433 (1966).

(5) H. C. Brown and J. D. Cleveland, *J. Amer. Chem. Soc.*, **88**, 2051 (1966).

(6) R. C. Hahn, T. F. Corbin, and H. Shechter, *ibid.*, **90**, 3404 (1968).

TABLE I

SOLVOLYSIS RATES OF SUBSTITUTED CUMYL *p*-NITROBENZOATES AT VARIOUS TEMPERATURES AND SOLVENT COMPOSITIONS

Substituent	Solvent compn, w/w	Temp, °C	$k \times 10^5$, sec^{-1}
p-Methyl	60% aq acetone	46.4	1.84 ± 0.05
p-Hydrogen			0.746 ± 0.007
p-Allyl			7.49 ± 0.06
p-*t*-Butyl			11.8 ± 0.2
p-Chloro			0.220 ± 0.004
p-γ,γ-Dimethylallyl			11.8 ± 0.1
m-Allyl			0.858 ± 0.005
p-3-Butenyl			12.7 ± 0.3
p-Methyl	50% aq acetone		61.4 ± 0.2
p-Hydrogen			2.63 ± 0.03
p-Allyl			24.7 ± 0.1
p-*t*-Butyl			36.1 ± 0.3
p-γ,γ-Dimethylallyl			39.0 ± 0.5
m-Allyl			2.65 ± 0.02
p-3-Butenyl			38.7 ± 0.3
p-Methyl		38.0	24.6 ± 0.4
p-Hydrogen			0.879 ± 0.018
p-Allyl			9.72 ± 0.10
p-*t*-Butyl			15.0 ± 0.1
p-γ,γ-Dimethylallyl			15.4 ± 0.2
m-Allyl			1.20 ± 0.01
p-3-Butenyl			15.6 ± 0.2
p-Allyl		30.0	3.87 ± 0.01
p-γ,γ-Dimethylallyl			6.15 ± 0.06
p-3-Butenyl			5.92 ± 0.06
p-Allyl	60% aq acetone	46.4	8.00 ± 0.08[a]
p-γ,γ-Dideuterioallyl			7.97 ± 0.09[a]
p-α,α-Dimethylallyl			6.71 ± 0.08[a]

[a] Determined by V. K. Jones.

TABLE II

SUBSTITUENT CONSTANTS FOR ALLYLIC AND SEVERAL REFERENCE SUBSTITUENTS

Substituent	σ^+
H	0.00[a]
p-Ethyl	−0.291[b]
m-Ethyl	−0.063[b]
p-Allyl	−0.221[c]
m-Allyl	−0.023[c]
p-γ,γ-Dimethylallyl	−0.262[c]
p-3-Butenyl	−0.262[c]
p-*t*-Butyl	−0.256[b]
p-α,α-Dimethylallyl	−0.212[c]
p-Cyclopropyl	−0.410[d]

[a] By definition. [b] Y. Okamoto and H. C. Brown, *J. Amer. Chem. Soc.*, 79, 1913 (1957). [c] Determined in this study. [d] Reference 4.

tion. Data for the *p*-methyl compound is included for comparative purposes. These data are indicative of a common mechanism for reaction of each compound involving ionization in the slow step.

Discussion

The σ^+ relationship defined by Brown and Okamoto[7] provides a probe for measuring electronic changes in a carbonium ion reaction as a function of substituents suitably located to allow for conjugative interaction. The magnitude of the σ^+ constant for any given substituent is proportional to its ability to interact with a

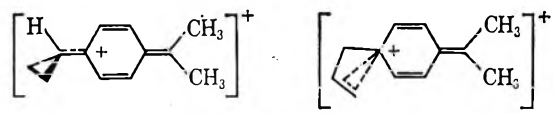
(7) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 485 (1957); *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

TABLE III

ACTIVATION PARAMETERS FOR THE SOLVOLYSIS OF METHYL, ALLYL, AND SUBSTITUTED ALLYL CUMYL *p*-NITROBENZOATES IN 50% AQUEOUS ACETONE AT 30.0°

Substituent	$E_{act.}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
p-Methyl	20.2	19.6	−18.2
p-Allyl	21.2	20.6	−20.1
p-γ,γ-Dimethylallyl	20.6	20.0	−19.3
p-3-Butenyl	20.6	20.0	−19.2
m-Allyl	23.1	22.6	−24.4

developing positive charge. It has been demonstrated that the *p*-cyclopropyl group is a more effective electron-donating substituent (σ^+ −0.410[4]) than other alkyl groups, as long as it can assume the required conformation[5] as in structure **1**. It was, therefore, anticipated that *p*-allyl substituents would also exhibit enhanced σ^+ constants, since the groups could interact with the developing positive charge on the *para* carbon of the aromatic ring *via* homoallylic participation **2**.[3]



1 **2**

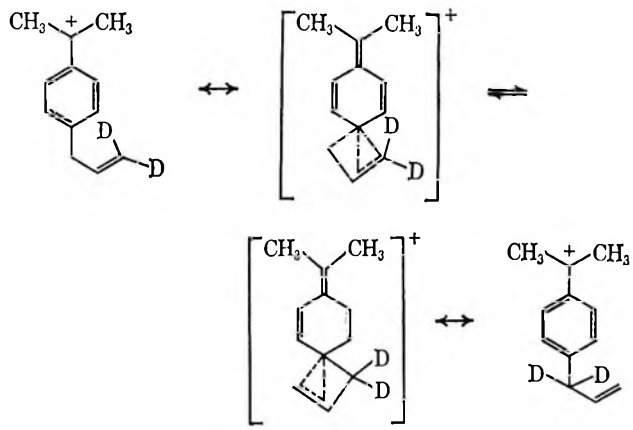
The effect of replacing a terminal methyl group in each alkyl substituent listed in Table II by a vinyl group is to render the unsaturated substituent less electron supplying. Such observations reflect the electron-withdrawing inductive effect of the π cloud of the alkenyl substituents. When the double bond is moved further from the benzene ring (*e.g.*, 3-butenyl), the inductive effect is felt less strongly and the σ^+ value becomes more negative (*i.e.*, the 3-butenyl substituent more effectively stabilizes a positive charge in this system than does the allyl group).

It must be pointed out, however, that the dominant influence of inductive effects in allyl substituents does not necessarily rule out homoallylic participation (resonance interaction). For example, studies of the hydration of divinylbenzenes[8] demonstrated that a vinyl substituent in a *meta* position was electron withdrawing (σ_m^+ +0.146) whereas a *p*-vinyl substituent was electron donating (σ_p^+ −0.152). This large difference ($\sigma_p^+ - \sigma_m^+$) must reflect a significant resonance-donating effect of the double bond even though the combined resonance and inductive effect of the *p*-vinyl group renders it less electron donating than the corresponding saturated group ($\sigma_p^+{}_{ethyl}$ −0.291). To determine whether a similar situation existed for allyl substituents, two types of studies were carried out. These consisted of kinetic isotope effect measurements and detailed product analyses.

Homoallylic participation of the allyl group could, in principle, lead to carbon skeletal rearrangement. To investigate this possibility *p*-γ,γ-dideuterioallylcumyl *p*-nitrobenzoate was prepared and subjected to solvolytic conditions. Detailed product and nmr studies indicated the complete absence of any rearrangement. Similarly, the kinetic isotope effect for γ,γ-dideuteration

(8) Unpublished observations of L. B. Jones and S. S. Eng.

of the *p*-allyl group was determined to be k_H/k_D = 1.00. These data are inconsistent with any significant incipient bond formation between the π cloud of the substituent and the aromatic ring.



The most consistent interpretation of these studies is that allyl substituents, in contrast to *p*-cyclopropyl, interact predominantly by an inductive interaction mechanism.

Experimental Section[9]

Materials.—Mallinckrodt AR acetone was refluxed with potassium permanganate until the color persisted and was then distilled. Magnesium turnings and dry ether were both Mallinckrodt AR. The *p*-dibromobenzene, *p*-bromoanisole, *p*-bromotoluene, and bromobenzene were Matheson AR. *p*-Bromochlorobenzene, *t*-butylbenzene, and *p*-chlorobenzyl chloride were obtained from Aldrich Chemical Co. All were used as received. Eastman practical grade allyl bromide was stirred over calcium chloride and distilled before use. Magnesium sulfate was used as the drying agent unless otherwise noted.

***p*-*t*-Butylbromobenzene.**—*t*-Butylbenzene (100 g, 0.745 mol) and 6.1 g of iron filings were placed in a 500-ml round-bottom flask equipped with a magnetic stirrer, thermometer, addition funnel, and condenser fitted with a hydrogen bromide trap. Bromine (131 g, 0.820 mol) was then added dropwise over a 2-hr interval during which time the temperature was maintained at 30°. The solution was then stirred overnight at room temperature. An equal volume of ether was added, and the mixture was extracted with successive portions of sodium bisulfite, sodium bicarbonate, and water. The solution was dried (potassium carbonate), concentrated, and distilled to give 87 g (55%) of *p*-*t*-butylbromobenzene: bp 130–133° (20 mm); $n^{27}D$ 1.5300 [lit.[10] bp 101–103.5° (11 mm); $n^{27}D$ 1.5304].

γ,γ-Dimethylallyl Chloride.—The procedure of Ultée was used.[11] A solution of 477 g (7.0 mol) of isoprene (Eastman White Label) and 100 ml of dry ether was cooled to −70°. Dry hydrogen chloride was then bubbled into the solution until 170 g had been added. The reaction mixture was allowed to stand overnight at Dry Ice temperature. The solution was then neutralized with anhydrous potassium carbonate, dried (calcium chloride), and distilled through a 4-ft Widmer column, yielding 220 g (30%) of γ,γ-dimethylallyl chloride, bp 45–60° (150 mm) [lit.[12] bp 67.2° (167 mm)].

1-(*p*-Chlorophenyl)-3-methyl-2-butene.—The Grignard reagent from 103.0 g (0.54 mol) of *p*-bromochlorobenzene and 13.1 g of magnesium turnings was prepared in 200 ml of dry ether by conventional techniques. The solution was cooled to 0° and 57.0 g (0.54) of γ,γ-dimethylallyl chloride in 100 ml of ether was added over 15 min. A two-phase system gradually developed, and, after 1 hr of stirring, the inorganic salts were granulated by dropwise addition of saturated aqueous ammonium chloride. The slurry was filtered, and the solids were washed with two 100-ml portions of ether. The washings and filtrate were combined, dried, concentrated, and distilled, yielding 40.8 g (42%) of 1-(*p*-chlorophenyl)-3-methyl-2-butene: bp 84–88° (1.5 mm); $n^{27}D$ 1.5303; nmr (CCl_4) δ 1.54 (d, 6 H, J = 4 Hz further split, J = 1 Hz, $-CH_3$), 3.08 (d, 2 H, J = 8 Hz, $-CH_2-$), 4.95–5.37 (t, 1 H, J = 8 Hz, further split into multiplet, J = 1 Hz, =CH–), 6.93 (M, 4 H, aromatic H).

This reaction, as well as the other coupling reactions to be described, has an induction period of 1–5 min. Care must be taken, therefore, during initial addition of halide to keep the reaction under control and prevent loss of material due to vigorous boiling.

***p*-Bromoallylbenzene.**—The Grignard reagent from 354 g (1.5 mol) of *p*-dibromobenzene and 40 g of magnesium turnings in 900 ml of ether was prepared by conventional techniques. A solution of 200 g (1.65 mol) of allyl bromide in 100 ml of ether was then added. Work-up as above with ammonium chloride followed by distillation of the concentrate yielded 193 g (65%) of *p*-bromoallylbenzene: bp 117–122° (19 mm); $n^{27}D$ 1.5507 [lit.[13] bp 95–96° (12 mm); $n^{20}D$ 1.520]; nmr (CCl_4) δ 3.01 (d, 2 H, J = 6 Hz, $-CH_2-$), 4.63–5.10 (m, 2 H, $=CH_2$), 5.35–6.20 (m, 1 H, –CH=), 6.50–7.45 (m, 4 H, aromatic H). Vpc analysis (GE SE-30) of the product indicated a 4% contamination of *p*-dibromobenzene.

3-(*p*-Chlorophenyl)-1-butene.—The Grignard reagent from 125 g (0.778 mol) of *p*-chlorobenzyl chloride and 19 g of magnesium turnings in 500 ml of ether was coupled as described above with a solution of 97 g (0.8 mol) of allyl bromide in 100 ml of ether. Distillation yielded 77.6 g (60%) of 3-(*p*-chlorophenyl)-1-butene: bp 59–61° (1.4 mm); $n^{27}D$ 1.5234; nmr (CCl_4) δ 1.82–2.63 (m, 4 H, $-CH_2CH_2-$), 4.53 (m, 1 H), 4.75 (m, 1 H), 5.11–5.80 (m, 1 H), 6.47–6.91 (m, 4 H, aromatic H).

***m*-Chloroallylbenzene.**—The Grignard reagent from 100 g (0.68 mol) of *m*-dichlorobenzene and 16.5 g of magnesium turnings in 110 ml of tetrahydrofuran[14] (THF) was coupled as described above with a solution of 84.8 g (0.70 mol) of allyl bromide in 30 ml of THF. Since magnesium halides are somewhat soluble in THF, 500 ml of pentane was added to precipitate them prior to addition of the saturated ammonium chloride solution. Distillation of the concentrate yielded 26 g (25%) of *m*-allylchlorobenzene: bp 60–65° (3 mm); $n^{27}D$ 1.5321; nmr (CCl_4) δ 2.65 (d, 2 H, J = 7 Hz, $-CH_2-$), 4.27 (m, 1 H), 4.50 (m, 1 H), 4.82–5.42 (m, 1 H), 6.09–6.58 (m, 4 H, aromatic H).

3-(*p*-Chlorophenyl)-3,3-dimethyl-1-butene.[15]—*p*-Chlorophenylacetone was prepared from 100 g (0.662 mol) of α-(*p*-Chlorophenyl)acetonitrile as described by Overberger and Biletch[16] to give 52 g (0.31 mol, 47%) of material: bp 98.5–102.5° (0.5 mm) [lit.[16] bp 100–101° (3 mm)]; nmr δ 1.9 (s, 3 H, $-CH_3$), 3.40 (s, 2 H, $-CH_2-$), and 7.0 (4 H, aromatic H).

To a stirred suspension of 12 g of sodium hydride (15% dispersion in mineral oil) in 120 ml of anhydrous 1,2-dimethoxyethane cooled in ice was added dropwise with stirring over 4 hr a solution of 29.0 g (0.713 mol) of *p*-chlorophenylacetone and 56 g (0.39 mol) of methyl iodide in 20 ml of anhydrous 1,2-dimethoxymethane. The mixture was stirred at room temperature overnight, then poured onto ice, and extracted with ether. The ether layer was dried, concentrated, and distilled to give 28 g (0.143 mol, 82%) of 1-(*p*-chlorophenyl)-,1,1-dimethyl-2-propanone: bp 102–104° (1 mm); nmr δ 1.20 (s, 6 H, *gem*-dimethyl), 1.70 (s, 3 H, CH_3), and 6.92 (4 H, aromatic H).

Reduction of 28 g (0.143 mol) of 1-(*p*-chlorophenyl)-1,1-dimethyl-2-propanone with excess lithium aluminum hydride yielded 25 g of the crude alcohol, which was acetylated without further purification with 25 g of acetyl chloride in pyridine to give

(9) Melting points were determined with a Mel-Temp capillary apparatus and are uncorrected. Nmr spectra were determined in CCl_4 solution with Varian A-60 and HA-100 spectrometers using external and internal tetramethylsilane, respectively, as standards. Infrared spectra were determined with a Perkin-Elmer Model 337 using neat samples between sodium chloride plates. Ultraviolet spectra were obtained on a Cary Model 14 spectrometer. Gas chromatography was performed on a Wilkins Model A-90, P-3 chromatograph. The columns used were a 5-ft 5% FFAP on 60–80 Chromosorb P, and an 8-ft 18% GE SE-30 on base-washed Chromosorb P. Microanalyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo.

(10) J. R. B. Boocock and W. J. Hickinbottom, *J. Chem. Soc.*, 2587 (1961).

(11) A. J. Ultée, *ibid.*, 530 (1948).

(12) W. G. Young, S. Winstein, and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 1968 (1951).

(13) K. C. Frisch, *J. Polym. Sci.*, **41**, 359 (1959).

(14) H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. J. Cserr, *J. Org. Chem.*, **22**, 1202 (1957).

(15) Synthesized by Vera K. Jones.

(16) C. G. Overberger and H. Biletch, *J. Amer. Chem. Soc.*, **73**, 4880 (1951).

TABLE IV

PHYSICAL CONSTANTS AND STARTING HALIDES OF *para*-SUBSTITUTED 2-PHENYL-2-PROPANOLS

Substituted 2-phenyl-2-propanols	Registry no.	Parent compd	Mp, °C	Bp, °C (mm)	$n^{27}D$
p-Hydrogen	617-94-7	Bromobenzene		60–65 (4.0)	1.5102
p-Methyl	1197-01-9	*p*-Bromotoluene		76–78 (2.0)	1.5128
p-*t*-Butyl	23853-82-9	*p*-Bromo-*t*-butylbenzene	76–78		
p-Methoxy	7428-99-1	*p*-Bromoanisole		85–90 (0.5)	1.5263
p-Allyl	22975-61-7	*p*-Bromoallylbenzene		70–75 (0.2)	1.5217
p-Chloro	1989-25-9	*p*-Bromochlorobenzene	42–43	98–103 (4.0)	1.5339
p-γ,γ-Dimethylallyl	23853-86-3	*p*-γ,γ-Dimethylallylchlorobenzene		85–95 (0.5)	1.5247
m-Allyl	23853-87-4	*m*-Allylchlorobenzene		74–77 (3.0)	1.5186
p-3-Butenyl	23853-88-5	*p*-3-Butenylbromobenzene		104–107 (0.45)	1.5184

TABLE V

MELTING POINTS, ABSORPTION MAXIMA, AND CHEMICAL ANALYSES OF CUMYL *p*-NITROBENZOATES

para substituent	Registry no.	Mp, °C	λ_{max} (log ϵ)	% C Calcd	% C Found	% H Calcd	% H Found
Hydrogen	7429-06-3	132.5–133.5	259 (3.102)				
p-Methyl	23852-75-7	105–107	259 (3.105)				
p-Methoxyl	23852-76-8	88–91					
p-*t*-Butyl	23852-77-9	114–116	260 (3.114)				
p-Chloro	23852-78-0	133–134.5	259 (3.108)				
p-Allyl	23852-79-1	45.4–46.1	260 (3.109)	70.14	70.04	5.89	5.91
m-Allyl	23852-80-4	66–67	260 (3.110)	70.14	69.94	5.89	5.83
p-3-Butenyl	23852-81-5	69–69.5	260 (3.107)	70.78	70.63	6.24	6.22
p-γ,γ-Dimethylallyl	23852-82-6	71.0–71.8	258 (3.102)	71.37	71.53	6.56	6.65

25 g (0.1 mol, 80%) of the corresponding acetate: bp 126–128° (1.2 mm); nmr δ 1.02 (d, 2 H, J = 8 Hz, $-CH_3$), 13.8 (s, 6 H, *gem*-dimethyl), 2.02 (s, 3 H, $-COCH_3$), 5.22 (q, 1 H, J = 8 Hz), and 7.48 (s, 4 H, aromatic H); ir 1735 cm^{-1} (ester C=O).

Pyrolysis of 24 g of the acetate at 450–500° gave 11.5 g (0.64 mol, 64%) of a colorless liquid: bp 60–65° (0.6 mm); nmr δ 1.32 (s, 6 H, *gem*-dimethyl), 4.8–6.3 (m, 3 H, olefinic H), and 7.30 (s, 4 H, aromatic); ir 3065 cm^{-1} (olefinic CH) and no absorption at 1700–1750 cm^{-1}.

2-Phenyl-2-propanol.—The Grignard reagent from 157.0 g (1.0 mol) of bromobenzene and 24.3 g of magnesium in 500 ml of ether was prepared by conventional techniques. A solution of 58 g (1.0 mol) of acetone in 100 ml of ether was added with cooling. After a short period of stirring, the alkoxide salts were destroyed by adding a saturated ammonium chloride solution until a heavy granular precipitate formed. The solution was filtered, the salts were washed with two 100-ml portions of ether, and the washings and filtrate were combined, dried, and concentrated. Distillation of the residual oil from potassium carbonate in base-washed glassware yielded 67 g (50%) of 2-phenyl-2-propanol, bp 60–65° (4 mm).

The same general procedure was employed in the synthesis of the other substituted phenyldimethylcarbinols. THF was used as the solvent to prepare the arylmagnesium chlorides.

Table IV lists the starting aryl compound as well as the physical constants of these alcohols. Nmr spectra of all the alcohols were consistent with structure and, where available, the physical constants were in agreement with literature values.[17]

Conversion of Alcohols to *p*-Nitrobenzoates.—Although minor variations were used from alcohol to alcohol, the following procedure for 2-(*p*-chlorophenyl)-2-propyl *p*-nitrobenzoate is a typical example. Hereafter the alcohol portion of the esters will be named according to the cumyl system.

A solution of 17.0 g (0.1 mol) of *p*-chlorocumyl alcohol in 100 ml of dry pyridine was cooled to 0° and 18.6 g (0.1 mol) of *p*-nitrobenzoyl chloride (freshly recrystallized from CCl_4) was added in portions. After stirring for 24 hr at 0°, the solution was poured into a cold mixture of 200 ml of 3 *N* hydrochloric acid and 200 ml of pentane. The solution was filtered, the organic layer of the filtrate was separated, and the aqueous layer was extracted with two 100-ml portions of pentane. The pentane solutions were combined and washed with successive 100-ml portions of cold 3 *N* hydrochloric acid, saturated sodium bicarbonate, and water. Drying and concentrating yielded an oil which was crystallized by trituration with cold pentane. Recrystallization from hexane yielded 18.1 g (57%) of *p*-chlorocumyl *p*-nitrobenzoate: mp 133–134.5°; λ_{max} (C_2H_5OH) 259 nm (log ϵ 3.108); nmr (CCl_4) 2.08 (s, 6 H, *gem*-dimethyl), 7.44 (s, 4 H, cumyl ring aromatic H), 8.39 (s, 4 H, *p*-nitrobenzoyl H).

Table V lists melting points and uv absorbances for all esters synthesized and elemental analyses of the olefinic esters employed in this study. The nmr spectrum of each ester was similar to that reported above for *p*-chlorocumyl *p*-nitrobenzoate.

3-(*p*-Chlorophenyl)-1,1-dideuterio-1-propene.—Diethyl *p*-chlorobenzylmalonate was prepared by the procedure described by Barnes and Gordon[18] from 105 g (0.656 mol) of diethyl malonate, 34 g (0.5 mol) of sodium ethoxide, and 80.5 g (0.5 mol) of *p*-chlorobenzyl chloride in a yield of 70 g (0.246 mol, 49%), bp 145–150° (0.8 mm). Hydrolysis of 67 g (0.236 mol) of diethyl *p*-chlorobenzylmalonate by the procedure described[18] with 180 ml of concentrated hydrochloric acid and 12 ml of acetic acid yielded 33 g of β-4-chloropropionic acid, mp 118–119° (lit.[19] mp 120–122°). Esterification of 54 g (0.292 mol) of the acid by conversion to the acid chloride followed by reaction with ethanol yielded 45 g (0.21 mol, 72%) of ethyl β-4-chlorophenylpropionate, bp 110–112° (0.7 mm) [lit.[20] bp 99° (0.4 mm)].

A mixture of 4.3 g (0.099 mol) of lithium aluminum deuteride in 200 ml of ether was cooled to 0°, and a solution of 42 g (0.198 mol) of ethyl *p*-chlorophenylpropionate in 125 ml of ether was added dropwise with stirring and cooling. After addition, the mixture was stirred for 15 min; then consecutively and dropwise were added 4.2 g of water, 4.2 g of a 15% aqueous solution of sodium hydroxide, and 12.6 g of water. The mixture was stirred for 30 min. The solid was filtered and washed with ether. The ether layers were combined and dried over potassium carbonate, and volatile materials were removed by distillation on a steam bath, followed by heating the residue to 100° at 0.8-mm pressure.

The crude alcohol was dissolved in 140 ml of anhydrous pyridine and cooled to 0°; 22.5 g (0.287 mol) of acetyl chloride was added dropwise with stirring. After a short period the mixture was extracted with 150 ml of ether. The ether layer was washed with portions of cold 10% hydrochloric acid until the washings were acidic and then with saturated sodium bicarbonate solution. The organic layer was dried and concentrated on a steam bath. Residual traces of solvent were removed under vacuum

(17) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **79**, 1913 (1957); H. C. Brown, Y. Okamoto, and G. Ham, *ibid.*, **79**, 1906 (1957); H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *ibid.*, **79**, 1897 (1957).

(18) R. A. Barnes and L. Gordon, *ibid.*, **71**, 2644 (1949).

(19) K. Kindler, H. G. Helling, and E. Sussner, *Ann.*, **505**, 200 (1957).

(20) R. Fuchs and J. A. Caputo, *J. Org. Chem.*, **31**, 1524 (1966).

(0.9 mm) at 50° to give 38.5 g of crude 3-(*p*-chlorophenyl)-1,1-dideuteriopropionyl acetate.

The crude acetate was pyrolyzed at 600°. Distillation of the pyrolysate yielded 18.7 g (0.121 mol, 61% based on ethyl *p*-chlorophenylpropionate) of 3-(*p*-chlorophenyl)-1,1-dideuterio-1-propene, bp 46–50° (1.4 mm). Gas chromatography[21] showed the material to be 90% pure: nmr δ 2.73 (d, 6 H, J = 7 Hz), 5.15–5.50 (2 H, olefinic H), and 6.25–6.80 (4.5 H, aromatic H).

p-(γ,γ-Dideuterioallyl)cumyl *p*-Nitrobenzoate.[15]—The Grignard reagent prepared from 5.0 g (0.038 mol) of 3-(*p*-chlorophenyl)-1,1-dideuterio-1-propene and 1.2 g (0.049 g-atom) of magnesium in 9 g of anhydrous tetrahydrofuran was allowed to react with excess acetone to give 3.2 g of material, bp 105–115° (1.5 mm). Gas chromatography[22] of the material showed *ca.* 85% one peak which had retention time identical with that observed upon chromatography of the nondeuterated analog. Ir spectra of distilled material showed strong OH absorption. Ir spectra of material collected by gas chromatography showed no OH absorption; *i.e.*, dehydration had occurred upon gas chromatography. Mass spectral analysis of the deuterated and nondeuterated olefins obtained by gas chromatography of the deuterated and nondeuterated alcohols showed the following composition for the deuterated anlog: 0.9% d_0, 4.9% d_1, 92% d_2, 0.7% d_3, 1.3% d_4.

Reaction of 3.2 g (0.018 mol) of the alcohol with 5.0 g (0.027 mol) of *p*-nitrobenzoyl chloride in 15 ml of pyridine yielded after normal work-up and recrystallization from pentane 2.66 g (0.0081 mol, 45%) of material, mp 38–39°. Two recrystallizations from pentane and drying under vacuum yielded material having mp 43.5–44° (cor) which was used for the kinetic measurements; nmr δ 3.30 (d, 2 H, J = 7 Hz), 5.7–6.0 (1 H, olefinic H), 7.0–7.34 (4 H, aromatic H), and 8.15 (4 H, aromatic H). No absorption was observed at 5 ppm where the nondeuterated derivative shows 2 H absorption.

Kinetic Procedure.—The desired amount of ester was dissolved in a preweighed quantity of acetone in a 100-ml volumetric flask, and the required weight of distilled, carbonate-free water was then added with shaking. The flask was placed in a thermostated bath and allowed to equilibrate for 15 min. In those cases where the half-life was less than 30 min, the solvents were preequilibrated at the bath temperature before mixing. At appropriate time intervals, 9-ml samples were removed and quenched with 10 ml of acetone at 0°, and the free *p*-nitrobenzoic acid was titrated with approximately 0.02 *N* sodium hydroxide using bromthymol blue as indicator. Infinity titers were taken after at least ten times the estimated half-life. Temperatures in all cases were controlled to at least ±0.03°.

Product Studies.—A solution of 0.307 g of *p*-allylcumyl *p*-nitrobenzoate in 100 ml of 50% w/w aqueous acetone was allowed to stand for 2 weeks at room temperature. After removing the acetone under reduced pressure, the aqueous residue was made basic with sodium bicarbonate, and the resultant solution was extracted with three 20-ml portions of ether. The extracts were combined, washed once with water, dried, and concentrated. The small quantity of residual oil which remained (*ca.* 50 μl) was distilled in a Hickman still. Capillary nmr spectra (Varian HA-100 spectrometer) of the distillate proved to be identical with that of *p*-allylcumyl alcohol. The infrared spectrum and retention times of the material upon vapor phase chromatography using GE SE-30 and FFAP liquid phases were identical with that of *p*-allylcumyl alcohol. No other components were detectable in the distillate. The pot residue had a melting point of 235–240°, undepressed on mixture with an authentic sample of *p*-nitrobenzoic acid.

In similar experiments, *p*-γ,γ-dimethylallyl-, *m*-allyl-, *p*-3-butenyl-, *p*-α,α-dimethylallyl-, and *p*-γ,γ-dideuterioallylcumyl *p*-nitrobenzoates were solvolyzed in an identical manner. Isolation of the product alcohols again proved rearrangement had not occurred by virtue of nmr, infrared, and gas chromatographic comparisons with authentic samples.

(21) A column packed with DC 710 on Gas-Chrom Q was employed.

(22) A column packed with Carbowax 20M on base-washed Chromosorb P was employed.

Registry No.—1-(*p*-Chlorophenyl)-3-methyl-2-butene, 23853-76-1; *p*-bromoallylbenzene, 2294-43-1; 3-(*p*-chlorophenyl)-1-butene, 23853-78-3; *m*-allylchlorobenzene, 3840-17-3; 3-(*p*-chlorophenyl)-3,3-dimethyl-1-butene, 1-(*p*-chlorophenyl)-1,1-dimethyl-2-propanone, 16703-39-2; 1-(*p*-chlorophenyl)-1,1-dimethyl-2-propanol (acetate), 23890-37-1; 3-(*p*-chlorophenyl)-1,1-dideuterio-1-propene, 23852-83-7; *p*-(γ,γ-dideuterioallyl)-cumyl *p*-nitrobenzoate, 23852-84-8.

Acknowledgment.—This work was supported in part by the Petroleum Research Fund, administered by the American Chemical Society. The authors are indebted to Dr. V. K. Jones for assistance with several aspects of this work.

Photochemical Transformations of Small-Ring Carbonyl Compounds. XXVI. Ground-State and Photochemical Reactions in the Thiacyclobutane Series[1,2]

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Reaction of α-bromomethylchalcone with sodium hydrosulfide gives 3-phenyl-4-benzoyl-1 2-dithiolane (**3**), 2,4-diphenyl-5-benzoyl-1,3-dithiane (**4**), and 2-phenyl-3,5-dibenzoylthiane (**5**). Oxidation of dithiolane **3** with peracid affords 3-phenyl-4-benzoyl-1,2-dithiolane 2,2-dioxide (**7**), which was thermolyzed in dilute solution to give *trans*-2-phenyl-3-benzoylthietane (**2**). When thiosulfonate **7** was pyrolyzed in the neat, a mixture of *trans*-α-methylchalcone and 3-phenyl-4-benzoyl-1,2-dithiolane (**3**) was obtained. Irradiation of either dithiolane **3**, thiosulfonate **7**, or thiacyclobutane **2** afforded a mixture of *cis*- and *trans*-benzalacetophenone. The low bond dissociation energy of the C–S bond appears to be the major factor responsible for the photolytic cleavage of these sulfur heterocycles.

Phenomena regarding excited states of small-ring nitrogen ketones have received considerable attention during the past few years.[4] Interest in these compounds has been aroused in part by theoretical studies and in part by the unusual rearrangements that occur upon irradiation.[5,6] The general types of phototrans-

(1) Part XXV: A. Padwa and W. Eisenberg, *J. Amer. Chem. Soc.*, **92**, 2590 (1970).

(2) For a preliminary report of this work, see A. Padwa and R. Gruber, *Chem. Commun.*, 5 (1969). This work was presented in part at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

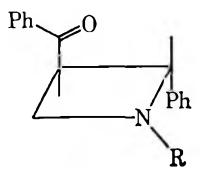
(3) Alfred P. Sloan Foundation Research Fellow, 1968–1970.

(4) For a review, see A. Padwa in "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 92.

(5) A. Padwa and L. Hamilton, *J. Amer. Chem. Soc.*, **89**, 102 (1967).

(6) A. Padwa and W. Eisenhardt, *ibid.*, **90**, 2442 (1968).

formations which have been observed with four-membered nitrogen ketones have been summarized in recent papers from this laboratory.[7-9] Evidence has been advanced in favor of a mechanism involving transfer of an electron from nitrogen to the triplet n → π* excited state. An intriguing question concerned the photochemical behavior of molecules of similar structure but possessing a different heteroatom as part of the ring. One such molecule is 2-phenyl-3-benzoylthietane (2), which is an analog of the much-studied arylaroylazetidine system (1). Not only is this system of interest because of its relationship to



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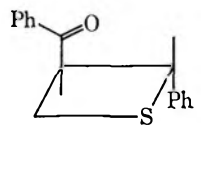
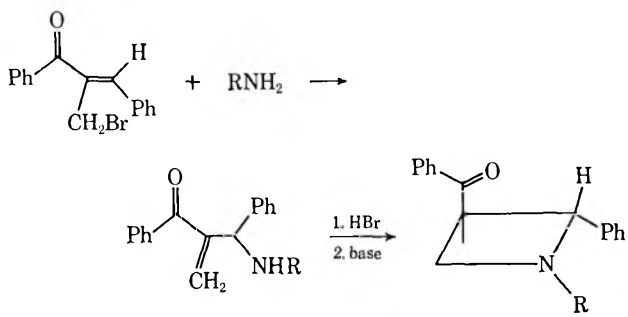


2

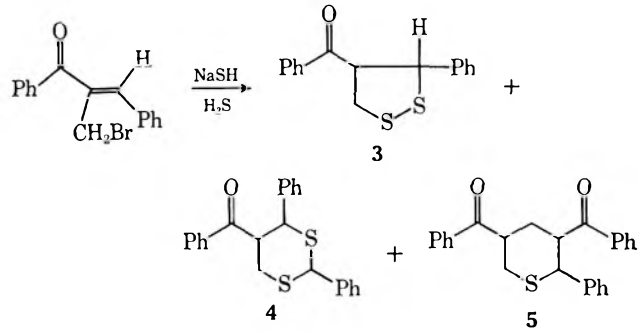
azetidine photochemistry, but also the possibility of electron transfer from sulfur was of intrinsic concern. The present paper reports on the photochemistry of several thiacyclobutane derivatives, as well as some of the interesting ground-state chemistry encountered with these systems.

Synthetic Aspects.—A synthesis of *trans*-2-phenyl-3-benzoylthietane (2) was required. Earlier reports in the literature have shown that 2-[α-(N-*t*-butylamino)benzyl]acrylophenone reacts with hydrogen bromide to give a β-aroyl-γ-bromoallylamine hydrobromide, which on treatment with base affords a substituted aroylazetidine in high yield.[10,11] In an attempt



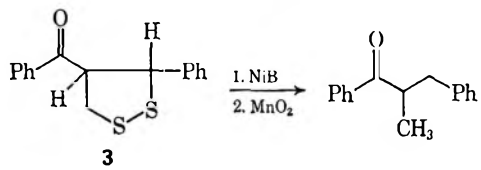
to prepare the related four-membered sulfur heterocycle by an analogous route, we treated α-bromomethylchalcone with sodium hydrosulfide. Our initial expectations for preparing the desired thietane ring were not realized, and instead the reaction proceeded to give three new products. These products were separated by chromatography on silica gel and were purified by recrystallization. The compounds are designated as **3**, **4**, and **5** and were formed in relative proportions of 36, 40, and 20%, respectively.

Compound **3** was shown to have the molecular formula $C_{16}H_{14}S_2O$, mp 81–82°. It showed bands in its



3 4 5

infrared spectrum at 6.01, 6.95, 7.78, 9.95, and 13.05 μ. The nmr spectrum ($CDCl_3$) showed an ABXY pattern: the AB part is centered at τ 6.50 and 6.25 (J_{AB} = 11.5 Hz, J_{AX} = J_{BX} = 7.5 Hz), the X proton appeared as a quartet at τ 5.53 (J_{XY} = 7.5 Hz), and the Y proton appeared as a doublet at τ 4.80 (J_{XY} = 7.5 Hz). A multiplet centered at τ 2.77 for ten aromatic protons was also evident. Simplification of the nmr spectrum could be readily achieved by heating compound **3** with sodium methoxide in CH_3OD. When this was done the nmr spectrum showed an AB pattern at τ 6.48 and a singlet at τ 4.80. This ready exchange implies that one proton is on a carbon atom adjacent to a carbonyl group. On the basis of these data and its origin, compound **3** is considered to be 3-phenyl-4-benzoyl-1,2-dithiolane. The assignment of structure **3** was confirmed in the following fashion. Desulfurization with nickel boride[12] followed by oxidation with activated manganese dioxide afforded 1,3-diphenyl-2-methylpropanone in high yield. The more stable *trans* structure is assigned to **3** in view of failure to detect any appreciable isomerism of **3** with sodium



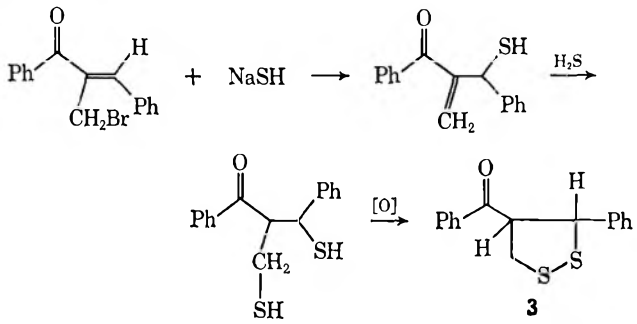
3

methoxide under conditions which exchanged the hydrogen atom α to the benzoyl group.

The formation of dithiolane **3** may be rationalized by assuming that sodium hydrosulfide first undergoes an S_N2' reaction with starting bromide and is then followed by further hydrogen sulfide addition across the conjugated double bond.[13,14] The intermediate dimercaptan undergoes subsequent oxidation to give the dithiolane ring. The oxidation of a dithiol to a disulfide has been previously described in the literature and can be accomplished by several methods.[15-17] Air oxidation in the presence of a trace of ferric ion was found to be among the best.[16,17] Other oxidizing agents that have been used to effect this conversion consist of iodine in alcohol, hydriodic acid in the presence of oxygen, and strong alkaline reagents in the presence

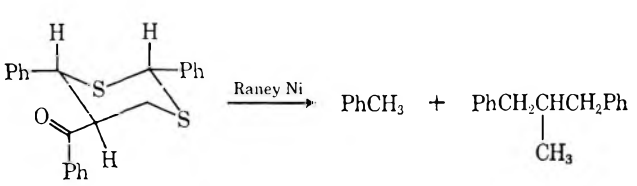
(7) A. Padwa, R. Gruber and L. Hamilton, *J. Amer. Chem. Soc.*, **89**, 3077 (1967).
(8) A. Padwa and R. Gruber, *ibid.*, **90**, 4456 (1969).
(9) A. Padwa and R. Gruber, *ibid.*, **92**, 107 (1970).
(10) R. P. Rebman and N. H. Cromwell, *Tetrahedron Lett.*, No. 52, 4833 (1965).
(11) J. L. Imbach, E. Doomes, R. P. Rebman, and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).
(12) W. E. Truce and F. M. Perry, *ibid.*, **30**, 1316 (1964).
(13) B. Lindberg and G. Bergson, *Ark. Kemi*, **23**, 319 (1965).
(14) B. H. Nicolet, *J. Amer. Chem. Soc.*, **57**, 1098 (1935).
(15) J. A. Barltrop, P. M. Hayes, and M. Calvin, *ibid.*, **76**, 4348 (1954).
(16) M. W. Bullock, J. J. Hand, and E. L. R. Stokslad, *ibid.*, **79**, 1975 (1957).
(17) M. W. Bullock, British Patent 796,894 (1958); *Chem. Abstr.*, **53**, 227 (1959).

of oxygen. The nature of the oxidizing reagent responsible for the formation of **3** is presently uncertain, although a reasonable possibility would be either ferric ion (present in the sodium hydrosulfide) or simply the aerated alkaline solution.



Compound **4**, mp 192–193°, which is the major product from the above reaction, is assigned the structure of 2,4-diphenyl-5-benzoyl-1,3-dithiane. This compound has the correct elemental analysis and molecular weight for $C_{23}H_{20}S_2O$, and has uv absorption similar to propiophenone. The nmr spectrum (100 MHz, CCl_4, see Figure 1) showed the expected magnetic nonequivalence of the methylene protons adjacent to the sulfur atom, there being the predicted eight-line multiplet (AB part of an ABXY system) centered at τ 6.72 and 6.88 with J_{AB} = 14 Hz, J_{AX} = 9 Hz, and J_{BX} = 4 Hz. The X proton consisted of a triplet of doublets centered at τ 5.73 with J_{XY} = 10 Hz. The remaining portion of the spectrum consisted of a doublet at τ 5.40 (J_{XY} = 10 Hz), a singlet at τ 4.60, and a multiplet for the aromatic hydrogens centered at τ 2.52. With values of the coupling constants available it was possible to determine the theoretical nmr spectrum using a variation of the frequint IV program of Bothner-By.[18] The calculated spectrum is given in Figure 1 along with the experimental 100-MHz spectrum. It is seen that the fit is excellent both in line position and intensity.

The fact that protons X and Y are coupled with J = 10 Hz, while the coupling constant for protons B and X is 4 Hz, suggests that the 4-phenyl and 5-benzoyl groups are in the equatorial position. This situation is similar to that found with other substituted dithiane systems.[19] Confirmation of the assignment of structure **4** was obtained by desulfurization of **4** with Raney nickel to give toluene and 1,3-diphenyl-2-methylpropane.



Determination of the elemental analysis and the molecular weight of compound **5** established its molecular formula as $C_{25}H_{22}SO_2$. The nmr spectrum (100 MHz) showed multiplets centered at τ 8.03 (2 H), 7.10 (2 H), and 2.75 (15 H), a triplet of triplets centered at τ 6.20 (1 H, J = 12 and 4.0 Hz), a triplet of doublets

(18) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **83**, 231 (1961).

(19) A. Ohno, Y. Ohnishi, and G. Tsuchihashi, *ibid.*, **91**, 5038 (1969).

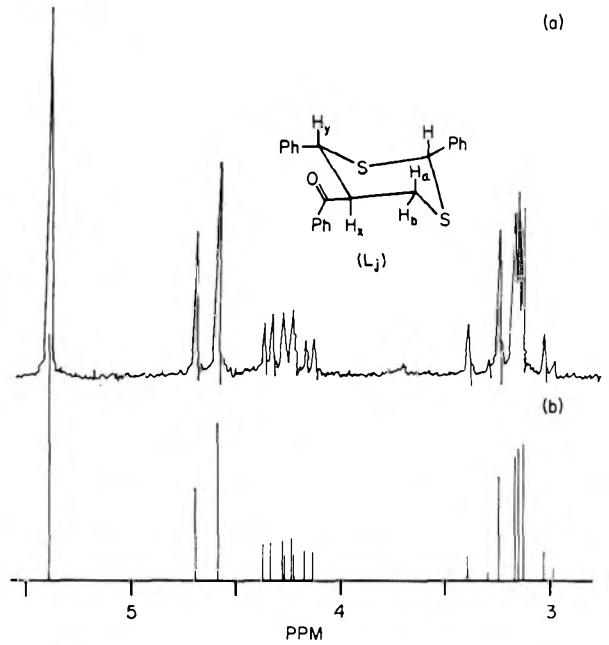


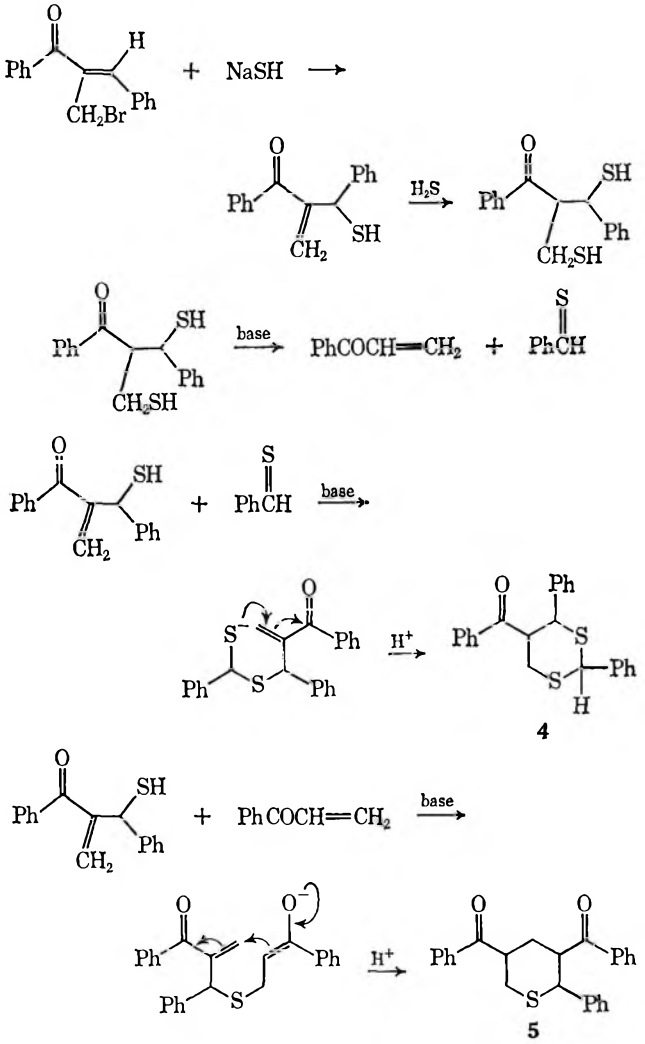
Figure 1.—Experimental (a) and calculated (b) 100-MHz spectrum of the ring protons of **4** in CCl_4.

centered at τ 5.85 (1 H, J = 10 and 4.0 Hz), and a doublet at τ 5.65 (1 H, J = 10 Hz). Simplification of the nmr spectrum could be achieved by refluxing **5** with sodium methoxide in CH_3OD. The nmr spectrum of the exchanged thiane showed two AB patterns at τ 7.90 (J = 14.0 Hz) and 7.07 (J = 14.0 Hz), a singlet at τ 5.60 (1 H), and a multiplet at τ 2.42. The sum of the available evidence requires that compound **5** have the structure of 2-phenyl-3,5-dibenzoylthiane (**5**). The location of all three substituents on the equatorial positions of the thiane ring is most consistent with the nmr data.

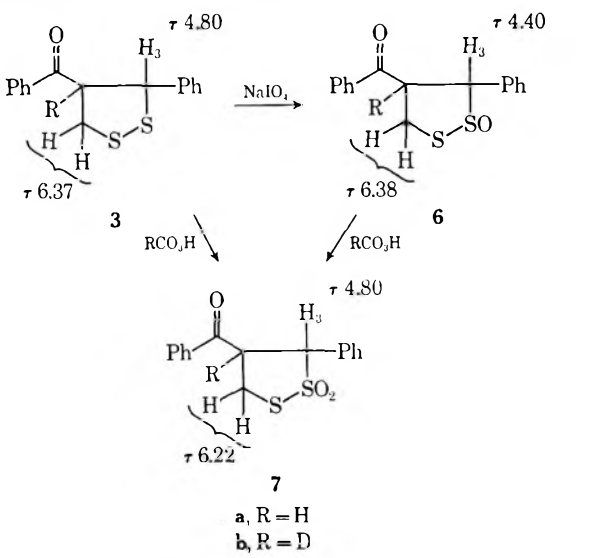
We return now to the consideration of the origin of products **4** and **5** from the reaction of α-bromomethylchalcone with sodium hydrosulfide. A reaction sequence that accounts for their formation is presented in Scheme I. In this scheme, the reaction proceeds to afford the dimercaptan as previously described for the formation of **3**. At this stage the dimercaptan can be oxidized to give **3** or else fragment to give thiobenzaldehyde and phenyl vinyl ketone. Further reaction of either of these two extremely reactive species with the unsaturated mercaptan would readily account for the formation of both **4** and **5**.

In view of the unexpected reactions encountered with the above system, our attention was further directed to the peracid oxidation of **3**, since the expected thiosulfonate **7** would possess a structure that could be desulfonated to the desired thiacyclobutane. Compound **3** was oxidized with sodium metaperiodate to **6**, mp 150–151°, in 86% yield. The infrared spectrum of dithiolane 2-oxide (**6**) exhibited a characteristic sulfoxide stretching frequency at 1070 cm^{-1}. The nmr of **6b** (R = D) showed a multiplet centered at τ 2.5 (10 H), a singlet at τ 4.40 (1 H, benzylic methine), and an unsymmetric quartet centered at τ 6.38 (2 H, methylene). Oxidation of **6b** (R = D) with *m*-chloroperbenzoic acid afforded thiosulfonate **7b** (R = D), mp 169–170°, in excellent yield. Typical sulfonyl stretching absorptions at 1300 and 1125 cm^{-1} were observed in the in-

SCHEME I



frared spectrum of compound **7b**. Its nmr spectrum showed absorptions at τ 2.45 (multiplet, 10 H, aromatic), 4.80 (singlet, 1 H, benzylic methine), and 6.22 (AB quartet, 2 H, methylene).

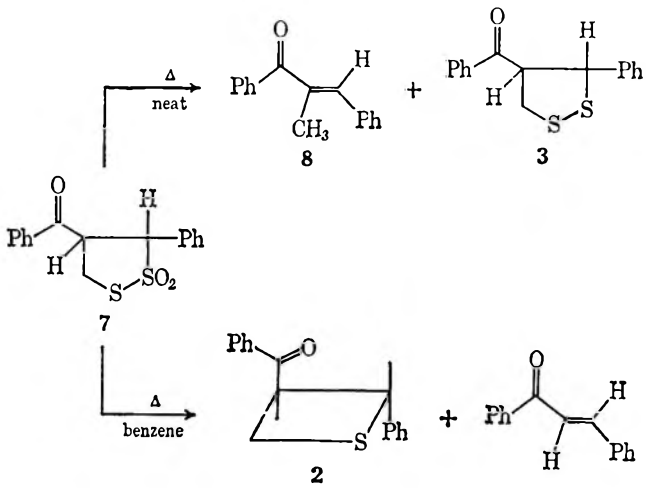


The stereochemical structure assignments for **6** and **7** rest on the following information. (A) Peracid oxidation of thiosulfinate **6** gave the same thiosulfonate as was obtained from **3**. This result demands that the same sulfur atom is always oxidized. It is interesting to note that this behavior contrasts with compounds of type $RS(CH_2)_nSOR$, where the sulfide sulfur atom is preferentially oxidized.[20-23] (B) The magnetic anisotropic effects of the sulfinyl function are such that protons *syn* to the S–O bond are deshielded and protons *anti* to the S–O linkage are shielded.[24,25] Thus proton H_3 in structure **6** must be *syn* to the S–O bond. (C) A comparison of the chemical shift of the methylene hydrogens of compounds **3**, **6**, and **7** reveals that the most deshielded methylene hydrogens are those of compound **7**. This observation is in agreement with the assumption that the sulfonyl moiety has a stronger electron-withdrawing inductive effect than the sulfinyl group.[26] It appears that the sulfinyl group has little effect on the chemical shift at the center of the AB quartet in **6** when compared with the equivalent quartet in the spectrum of disulfide **3**. (D) When a methanol solution of **3** was refluxed over anhydrous potassium carbonate for 2 days, conditions under which complete exchange of the acidic C-4 hydrogen occurred, only starting material was recovered. Therefore, **3**, **6**, and **7** must have the thermodynamically more stable *trans* arrangement of the benzoyl and phenyl moieties.

Recently, Fava and Koch reported that aryl arenethiosulfinates readily undergo thermal racemization *via* pyramidal inversion at sulfinyl sulfur.[27] It seemed to us that compound **6** should also racemize at elevated temperatures and that this racemization could be followed by variable-temperature nmr spectroscopy. When the nmr spectrum of **6** was recorded at a range of temperatures from 166 to −50°, the singlet at τ 4.40 did not change in chemical shift or intensity. Also, no new peaks appeared in the spectrum as the temperature was varied. There was no noticeable decomposition at the elevated temperatures employed. The nmr spectrum showed a slight modification of the AB quartet with decreasing temperature—it broadened slightly and became symmetrical. This change is tentatively ascribed to a retardation of conformer interconversions. Inversion of configuration of the sulfinyl sulfur, whether retarded by cooling or accelerated by heating, should have caused a decrease in intensity of the τ 4.40 singlet and the appearance of a new singlet at *ca.* 0.4–1 ppm upfield. The absence of such a shift leads us to conclude that, although asymmetric open-chain aryl arenethiosulfinates may undergo thermal racemization *via* pyramidal inversion at 50°, the cyclic thiolsulfinate **6** is configurationally stable up to 166°. At this time we cannot fully explain why open-chain asymmetric thiolsulfinates should be configurationally labile and the five-membered counterpart should not. Perhaps configurational stability is a function of ring size in sulfur heterocycles, as is the case with nitrogen heterocycles.[28,29]

(20) D. Barnard and E. J. Percy, *Chem. Ind.* (London), 1332 (1960).
(21) P. Allen, P. J. Berner, and E. R. Malinowski, *ibid.*, 1164 (1961).
(22) J. Cymerman and J. B. Willis, *J. Chem. Soc.*, 1332 (1951).
(23) C. Frisell and G. Bergson, *Ark. Kemi*, **25**, 263 (1965).
(24) J. A. Deyrup and C. L. Mayer, *J. Org. Chem.*, **34**, 175 (1969).
(25) A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *Chem. Commun.*, 881 (1967).
(26) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962.
(27) A. Fava and P. Koch, *J. Amer. Chem. Soc.*, **90**, 3867 (1968).
(28) S. J. Brois, *ibid.*, **90**, 506 (1968).
(29) J. M. Lehn and J. Wagner, *Chem. Commun.*, 148 (1968).

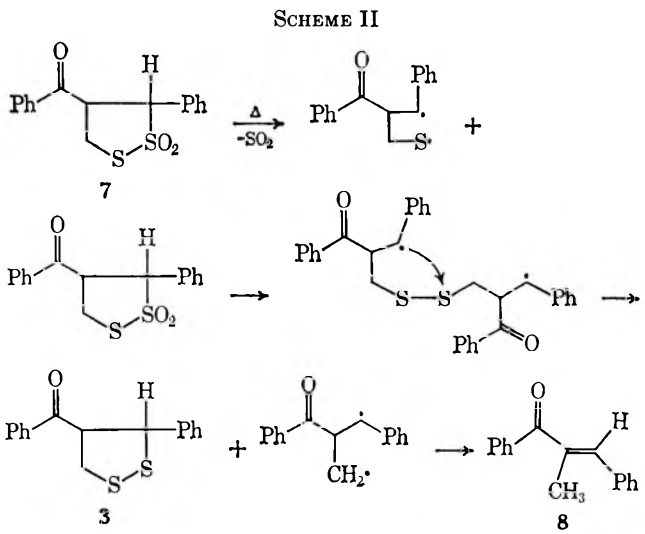
Thermal extrusion of sulfur dioxide from thiosulfonate **7** was readily achieved in a sealed tube at 225°. The pyrolysis afforded two major products, which were subsequently identified as *trans*-α-methylchalcone (**8**, 22%) and 3-phenyl-4-benzoyl-1,2-dithiolane (**3**, 29%). Under these conditions a significant amount of polymerization occurred. The failure to observe a product derived from loss of SO_2 on heating **7** at 225° led to an investigation of its behavior under slightly different pyrolytic conditions. When the thermolysis was carried out in a dilute benzene solution, two new products



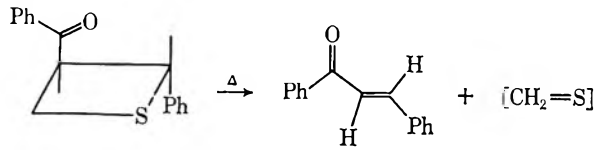
were isolated. The minor product was identified as *trans*-benzalacetophenone (38%). The major product (55%) was a colorless solid, mp 79–80°, having the composition $C_{16}H_{14}SO$. Chemical and spectral evidence (see Experimental Section) shows that this new compound is *trans*-2-phenyl-3-benzoylthietane (**2**).

The formation of **3** from the thermolysis of **7** can be envisaged as occurring *via* homolytic cleavage of the sulfur–sulfur bond followed by loss of sulfur dioxide. At high concentrations of starting material the resulting diradical may attack another molecule of thiosulfonate by an SH2 mechanism[30] as shown in Scheme II.

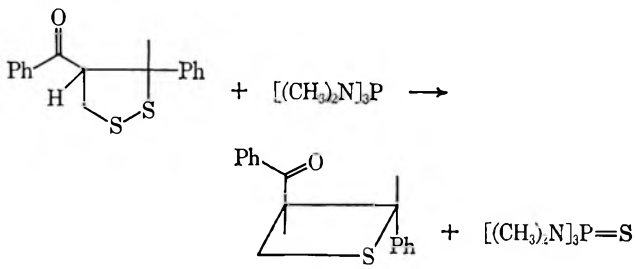
SCHEME II



The sequence of steps outlined above is not without precedent, as related SH2 reactions of disulfides have been reported with similar systems.[31–33] In addition, the isolation of *trans*-α-methylchalcone from the above reaction mixture lends considerable strength to the reaction sequence postulated in Scheme II. When the thermolysis was carried out in a dilute benzene solution the diradical prefers to undergo ring closure, thus accounting for the formation of thiacyclobutane **2**. Further fragmentation of **2** on heating has been shown to result in the formation of *trans*-benzalacetophenone and thioformaldehyde.



Preparation of the thietane ring by this route is subject to a number of variables, all of which must be carefully controlled in order to obtain even a moderate amount of product. In order to increase the yield of thiacyclobutane **2**, several alternate methods were tried. Truce recently reported that nickel boride would convert a disulfide into the corresponding sulfide.[12] It was further noted that nickel boride was inert toward sulfones. It seemed reasonable to attempt this reaction with dithiolane **3**. However, treatment of either **3** or **7** with nickel boride gave only 1,3-diphenyl-2-methylpropanol. An alternate procedure which involved the reaction of triphenyl phosphine with **3** in refluxing toluene resulted in ill-defined tars. By using a procedure recently described by Harpp and Snyder for the conversion of disulfides into sulfides, the desired thietane could be prepared in good yield.[34] Thus treatment of **3** with tris(dimethylamino) phosphine led to *trans*-2-phenyl-3-benzoylthietane (**2**) in 60% overall yield.



Photochemical Studies.—Although the ground-state chemistry of substituted thietanes has received considerable attention,[35] the photochemical transformations of this ring system have been virtually unexplored. It was of particular interest to ascertain the photochemical routes available to the thietane ring in order to make a comparison with the photochemistry of the azetidine system, which is known to give diarylpyrroles upon irradiation.[9] In particular, the influence of the heteroatom in the photochemistry of these four-membered rings needed to be assessed.

(30) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 51.

(31) C. Walling, O. H. Basedow, and E. S. Savas, *J. Amer. Chem. Soc.*, **82**, 2181 (1960).

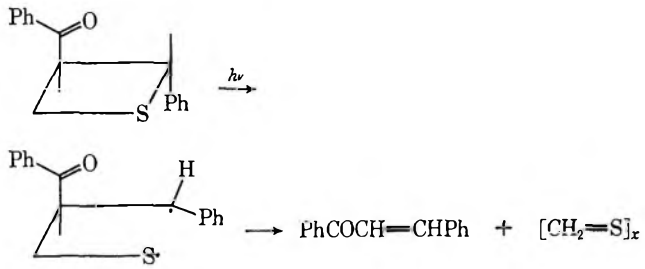
(32) A. V. Tobolsky and B. Baysal, *ibid.*, **75**, 1757 (1953).

(33) W. H. Stockmayer, R. O. Howard, and J. T. Clarke, *ibid.*, **75**, 1756 (1953).

(34) D. N. Harpp, J. G. Gleason, and J. P. Snyder, *ibid.*, **90**, 4181 (1968).

(35) Y. Etienne, R. Soulas, and H. Lumbroso, "Heterocyclic Compounds with Three and Four Membered Rings," Part II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 647.

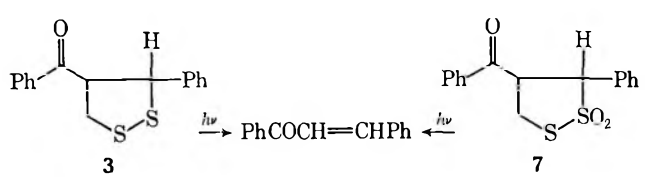
Exposure of a dilute solution of *trans*-2-phenyl-3-benzoylthietane (**2**) in 95% ethanol to a Hanovia 450-W mercury arc lamp for 3 hr resulted in the complete disappearance of **2** and clean conversion into a mixture of *cis*- and *trans*-benzalacetophenone. The anticipated 2,3- and 2,4-diphenylthiophene were not detected in the reaction mixture. This result indicates that the photochemistry of the thietane system proceeds by an entirely different path from that encountered in the azetidine series. The formation of *cis*- and *trans*-benzalacetophenone may be envisaged as proceeding by way of a homolytic cleavage of the benzylic carbon–sulfur bond. The resulting diradical undergoes subsequent fragmentation to thioformaldehyde and benzalacetophenone.



The low bond dissociation energy of the C–S bond may be the major factor responsible for the difference in photochemistry of the two heterocyclic systems. It is interesting to note that the reaction does not involve the extrusion of atomic sulfur as had been observed in the related episulfide system.[36]

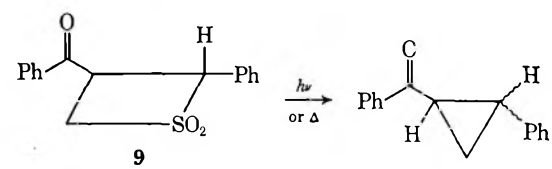
The photoconversion of **2** into *cis*- and *trans*-benzalacetophenone could not be quenched by piperylene or naphthalene. Addition of acetophenone or irradiation in dilute acetone solution unequivocally demonstrates that photosensitization is observed. These data indicate that the triplet state of **2** is capable of undergoing fragmentation to benzalacetophenone. The lack of quenching by piperylene or naphthalene denotes either that the singlet state can also lead to product or that a triplet intermediate is formed but is rapidly consumed by reaction prior to diffusion.

It was also found that irradiation of **3** or **7** in cyclohexane afforded a mixture of *cis*- and *trans*-benzalacetophenone. It seems reasonable to assume that these



reactions proceed *via* homolytic cleavage of the S–S bond, followed by loss of sulfur (or sulfur dioxide) to give the same diradical as was proposed earlier.

As an extension of our investigations on the photochemistry of the thiacyclobutane ring, the irradiation of *trans*-2-phenyl-3-benzoylthietane 1,1-dioxide (**9**) was investigated next. The photochemical decomposition of cyclic sulfones has been frequently reported in the literature.[37,38] Cava has adequately demonstrated the ease with which sulfur dioxide can be eliminated from sulfones upon irradiation.[37] Photolysis of a dilute solution of **9**, synthesized by the peracid oxidation of **2**, in cyclohexane gave a mixture of *cis*- and *trans*-1-phenyl-2-benzoylcyclopropane. Similar results were



obtained when **2** was pyrolyzed at 230°. An analogous case has been reported by Dodson and Klose,[39] who found that the pyrolysis of *cis*- and *trans*-diphenylthietane dioxide resulted in the formation of *cis*- and *trans*-diphenylcyclopropane. The better leaving ability of SO_2 compared with sulfur may account for the difference in the thermal and photochemical behavior of **2** *vs.* **9**.

Experimental Section

General.—Nmr spectra were recorded on a Varian A-60 spectrometer using carbon tetrachloride as solvent. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Gas–liquid partition chromatographic analyses and preparative separations were carried out using an F & M Model 5720 instrument equipped with a 6 ft × 0.25 in. 20% Apiezon M on 60–80 mesh Chromosorb W column. Irradiations were carried out using Hanovia 450- and 550-W, medium-pressure mercury lamps with water-cooled quartz immersion wells.

Reaction of *trans*-α-Bromomethylchalcone with Sodium Hydrosulfide.—A solution of 250 g (3.35 mol) of sodium hydrosulfide, dissolved in a sufficient amount of water to give a total volume of 340 ml, was rapidly added to a solution containing 40 g (0.133 mol) of *trans*-α-bromomethylchalcone in 3 l. of methyl alcohol. The resultant solution was heated to reflux for 10 min and hydrogen sulfide was introduced into the refluxing mixture for an additional 30 min. The yellow solution was diluted with 5 l. of cold water and carefully acidified with concentrated hydrochloric acid to pH 5. Extraction with carbon tetrachloride, followed by removal of the solvent under reduced pressure, gave 60 g of a yellow oil. Chromatography of 6.0 g of this material on a silica gel column (1.5 × 32 in.) resulted in the separation of the crude oil into three components. The first component eluted from the column with benzene amounted to 1.4 g of a yellow solid which was recrystallized from benzene to give 3-phenyl-4-benzoyl-1,2-dithiolane (**3**) as a yellow, crystalline solid, mp 81.5–82.5°, yield 36%.

Anal. Calcd for $C_{16}H_{14}S_2O$: C, 67.09; H, 4.93; S, 22.39. Found: C, 66.93; H, 4.89; S, 22.60.

The infrared spectrum was characterized by bands at 6.01, 6.95, 7.78, 9.95, and 13.05 μ. The nmr spectrum ($CDCl_3$) showed a ABXY pattern with the AB part centered at τ 6.50 and 6.25 (J_{AB} = 11.5 Hz, J_{AX} = J_{BX} = 7.5 Hz), the X proton at τ 5.53 (q, J_{XY} = 7.5 Hz), and the Y proton at τ 4.80 (d, J_{XY} = 7.5 Hz). A multiplet centered at τ 2.77 for ten aromatic protons was also evident. The molecular weight (ebullioscopic) in chloroform had a value of 273 (calcd, 286) in agreement with the proposed structure.

Simplification of the nmr spectrum could be readily achieved by replacement of the acidic α hydrogen with deuterium. A solution of 0.5 g of 3-phenyl-4-benzoyl-1,2-dithiolane and 0.5 g of anhydrous potassium carbonate in 18 ml of methanol-O-*d* was heated to reflux for 2 days. At the end of this time the reaction mixture was evaporated and the oily residue was purified by preparative thick layer chromatography to afford 0.24 g of a yellow solid, mp 80–81°. The nmr spectrum ($CDCl_3$) showed an AB pattern centered at τ 6.48 and a singlet at τ 4.88. The

(36) A. Padwa, D. Crumrine, and A. Shubber, *J. Amer. Chem. Soc.*, **88**, 3064 (1966).

(37) M. P. Cava, R. H. Schlessinger, and J. P. van Meter, *ibid.*, **86**, 3173 (1964).

(38) J. Saltiel and L. Metts, *ibid.*, **89**, 2223 (1967).

(39) R. M. Dodson and G. Klose, *Chem. Ind.* (London), 450 (1963).

quartet normally associated with the α hydrogen was completely absent. A similar experiment employing methanol gave only recovered starting material, thereby indicating that the thermodynamically more stable *trans* isomer was formed in the original reaction.

The second component eluted from the column (2% ethyl acetate–benzene) was recrystallized from benzene–heptane to give 2,4-diphenyl-5-benzoyl-1,3-dithiane (**4**) as a white, crystalline solid, mp 192–193°, yield 2.1 g (45%).

Anal. Calcd for $C_{23}H_{20}S_2O$: C, 73.36; H, 5.35; S, 17.03. Found: C, 73.12; H, 5.55; S, 16.66.

The infrared spectrum of this compound is characterized by bands at 6.00, 7.78, 8.40, 9.88, 12.95, 13.55, and 14.53 μ. The molecular weight (ebullioscopic) in chloroform had a value of 364 (calcd, 376). The 100-MHz nmr spectrum showed the expected magnetic nonequivalence of the methylene protons adjacent to the sulfur atom, there being the predicted eight-line multiplet (AB part of an ABXY system) centered at τ 6.72 and 6.88 with J_{AB} = 14 Hz, J_{AX} = 9 Hz, and J_{BX} = 4 Hz. The X proton of the ABXY system consisted of a triplet of doublets centered at τ 5.73 with J_{XY} = 10 Hz. The remaining portion of the spectrum consisted of a doublet at τ 5.40 (J_{XY} = 10 Hz), a singlet at τ 4.60, and a multiplet for the aromatic hydrogens centered at τ 2.52.

The third material isolated from the chromatography column with 3% ethyl acetate–benzene was crystallized from ethyl acetate to give 2-phenyl-3,5-dibenzoylthiane (**5**) as a white, crystalline solid, mp 180–181°, yield 1.1 g (20%).

Anal. Calcd for $C_{25}H_{22}SO_2$: C, 77.68; H, 5.73; S, 8.27. Found: C, 77.68; H, 5.75; S, 8.31.

The infrared spectrum was characterized by bands at 5.95, 6.02 (split), 6.95, 7.88, 12.85, and 14.54 μ. The molecular weight (ebullioscopic) in chloroform had a value of 378 (calcd, 386). The 100-MHz nmr spectrum ($CDCl_3$) showed multiplets centered at τ 8.03 (2 H), 7.10 (2 H), and 2.75 (12 H), a triplet of triplets centered at τ 6.20 (1 H, J = 12 and 4.0 Hz), a triplet of doublets centered at τ 5.85 (1 H, J = 10 and 4.0 Hz), a doublet at τ 5.65 (1 H, J = 10 Hz), and a doublet of split doublets at τ 2.10 (2 H, J = 1.0 Hz) and 2.32 (2 H, J = 1.0 Hz). The latter two signals are assigned to the *ortho* hydrogens on the benzoyl ring.

Simplification of the nmr spectrum could be achieved by replacement of the acidic α hydrogens with deuterium. A solution of 1.0 g of **5** and 0.1 g of sodium metal in 25 ml of methanol-O-*d* was heated to reflux for 2 days. At the end of this time the reaction mixture was evaporated and the residue was subjected to the exchange conditions for an additional three cycles. After the third cycle the residue was crystallized from ethyl acetate to afford a white solid, mp 180–181°, yield 0.3 g. The nmr spectrum of the exchanged thiane showed two AB patterns centered at τ 7.90 (J = 14.0 Hz) and 7.07 (J = 14.0 Hz), a singlet at τ 5.60, and a multiplet centered at τ 2.42.

Nickel Boride Desulfurization of 3-Phenyl-4-benzoyl-1,2-dithiolane (3).—The desulfurization of **3** was carried out according to the procedure of Truce and Perry.[12] A solution of 1.88 g (0.049 mol) of sodium boride in 20 ml of water was added dropwise to an ice-cooled solution of 3.9 g (0.0165 mol) of nickel(II) chloride hexahydrate and 0.44 g (1.65 mmol) of **3** in 100 ml of 95% ethanol. After the addition was complete the reaction was heated to reflux for 7 hr, cooled to 25°, and filtered. The filtrate was concentrated under reduced pressure to give a colorless oil. The infrared spectrum showed the presence of a strong hydroxyl group and a weak carbonyl band. This crude oil was dissolved in 200 ml of pentane and stirred at 25° with 5 g of activated manganese dioxide. After 36 hr the solution was filtered and the filtrate was concentrated to give a colorless oil. A short-path distillation at a pot temperature of 150° (0.12 mm) gave 0.30 g (88%) of a colorless oil which was identical in all respects with an authentic sample of 1,3-diphenyl-2-methylpropanone.

An attempt was also made to carry out the desulfurization of **3** with Raney nickel. *Ca.* 10 g of Raney nickel (W. R. Grace and Co., No. 28) was added to 150 ml of ethanol containing 0.50 g of **3**. After the solution had been refluxed for 25 hr, the nickel was removed by filtration and the solvent was evaporated under reduced pressure. The residue was distilled and the fraction boiling at 94° (1.1 mm) was collected. This material (0.22 g) was identified as 1,3-diphenyl-2-methylpropane by comparison of its nmr and infrared spectra with those of an authentic sample.

Raney Nickel Desulfurization of 2,4-Diphenyl-5-benzoyl-1,3-dithiane (4).—Desulfurization of compound **4** was accomplished by refluxing a solution containing 0.55 g of **4** and 5.0 g of Raney nickel in 50 ml of methanol for 2 days. The excess Raney nickel was removed by filtration and the solvent was removed by a careful distillation. The distillate was diluted with 300 ml of water and then extracted with 10 ml of carbon disulfide. Gas chromatographic analysis of the carbon disulfide extracts showed the presence of two components that corresponded to solvent and toluene. The material with the same retention time as toluene was collected (10 ft × 0.25 in., 5% SE-30 column on Diatoport S at 100°) and comparison of its infrared spectrum with that of toluene established its identity. Distillation of the remaining residue gave a colorless oil which was identical in all respects with an authentic sample of 1,3-diphenyl-2-methylpropane.

3-Phenyl-4-benzoyl-1,2-dithiolane 2-Oxide (6).—To a solution of 2.0 g (0.007 mol) of 3-phenyl-4-benzoyl-1,2-dithiolane (**3**) in 175 ml of dioxane was added a solution of 1.5 g (0.007 mol) of sodium metaperiodate in 50 ml of water. After the solution had been allowed to stand at room temperature for 2 hr, a solid material precipitated which was subsequently filtered and discarded. The filtrate was evaporated under reduced pressure to give 1.92 g of a yellow solid. Recrystallization from benzene–heptane gave 3-phenyl-4-benzoyl-1,2-dithiolane 2-oxide (**6**) as a white, crystalline solid, mp 150–151°, yield 1.86 g (86%).

Anal. Calcd for $C_{16}H_{14}S_2O_2$: C, 63.54; H, 4.66; S, 21.20. Found: C, 63.40; H, 4.66; S, 20.89.

The infrared spectrum was characterized by bands at 5.95, 7.73, 7.89, 8.18, 9.35, 13.02, and 14.23 μ. The 100-MHz nmr spectrum ($CDCl_3$) showed multiplets centered at τ 6.38 (2 H) and 4.57 (1 H) and a doublet at τ 4.40 (1 H, J = 4.5 Hz).

3-Phenyl-4-benzoyl-1,2-dithiolane 2,2-Dioxide (7).—A solution of 5.0 g of 3-phenyl-4-benzoyl-1,2-dithiolane (**3**) and 7.6 g of 90% *m*-chloroperbenzoic acid in 300 ml of methylene chloride was allowed to stand at room temperature for 4 hr. At the end of this time the precipitated *m*-chlorobenzoic acid was removed by filtration and the solution was washed with 10% sodium carbonate and dried over magnesium sulfate. The solvent was removed under reduced pressure to leave a white solid. Recrystallization from benzene–heptane gave 3-phenyl-4-benzoyl-1,2-dithiolane 2,2-dioxide as a white, crystalline solid, mp 169–170°, yield 4.3 g.

Anal. Calcd for $C_{16}H_{14}S_2O_3$: C, 60.15; H, 4.41; S, 20.15. Found: C, 60.04; H, 4.40; S, 20.05.

The infrared spectrum was characterized by bands at 5.98, 7.70, 8.89, 10.01, 14.42, and 14.70 μ. The 100-MHz nmr spectrum ($CDCl_3$) showed multiplets centered at τ 6.22 (2 H), 5.12 (1 H), and 2.45 (10 H) and a doublet at τ 4.83 (1, H, J = 5.5 Hz).

Nickel boride desulfurization of dioxide **7** was carried out in a manner similar to that described for dithiolane **3**. The product obtained (95% yield) was identified as 1,3-diphenyl-2-methylpropanone by comparison with an authentic sample.

Peracid Oxidation of Dithiolane 2-Oxide (6) to Dithiolane 2,2-Dioxide (7).—A mixture of 0.48 g of 3-phenyl-4-benzoyl-1,2-dithiolane 2-oxide (**6**) and 0.34 g of 80% *m*-chloroperbenzoic acid in 130 ml of methylene chloride was allowed to stand at room temperature for 4 hr. At the end of this time, the precipitated *m*-chlorobenzoic acid was removed by filtration and the solution was extracted with 10% sodium carbonate and then dried over magnesium sulfate. The solvent was removed under reduced pressure, leaving a white solid. The infrared spectrum of the solid showed it to be a mixture of **6** and **7**. The crude solid was subjected to preparative thick layer chromatography. Chloroform extraction of the upper band followed by recrystallization of the solid from benzene–heptane afforded a crystalline solid, mp 168–170°, yield 0.30 g. The infrared spectrum of this component was identical with that of dioxide **7** prepared from the peracid oxidation of **3**. The mixture melting point of these two materials was undepressed at 169–170°. Evaporation of the chloroform extracts of the lower band gave a white solid which was identical in all respects with starting dithiolane 2-oxide (**6**).

Thermolysis of 3-Phenyl-4-benzoyl-1,2-dithiolane 2,2-Dioxide (7). A. **Neat.**—In a sealed Carius tube a 1.0-g sample of **7** was heated to 225° for 75 min. The dark oil obtained was dissolved in benzene and chromatographed on a Florisil column (1 × 20 in). Elution with 500 ml of benzene gave 0.20 g (29%) of 3-phenyl-4-benzoyl-1,2-dithiolane (**3**) as yellow needles, mp 80–81°. Further elution of the column with an additional 800 ml

of benzene gave 0.15 g (22%) of a yellow oil, whose nmr and infrared spectra were identical with those of an authentic sample of *trans*-α-methylchalcone. Further elution with 25% ethyl acetate–benzene afforded only ill-defined tars.

B. In Benzene.—A solution of 0.30 g of **7** in 30 ml of benzene was heated in a stainless steel tubular bomb at 230 ± 5° for exactly 75 min and then quickly cooled to room temperature. The solvent was removed under reduced pressure, leaving a light brown viscous oil. Preparative thick layer chromatography resulted in the separation of two distinct bands, which were taken up in chloroform. A yellow solid was isolated from the upper band, which, after recrystallization from 95% alcohol, afforded a white, crystalline solid, mp 79–80°, yield 0.13 g (55%). This material was assigned as *trans*-2-phenyl-3-benzoylthietane (**2**) on the basis of the following data.

Anal. Calcd for $C_{16}H_{14}SO$: C, 75.55; H, 5.54; S, 12.60. Found: C, 75.67; H, 5.59; S, 12.54.

The infrared spectrum was characterized by bands at 6.02, 7.01, 8.28, 8.95, 11.85, and 14.65 μ. The nmr spectrum (CCl_4) showed a multiplet centered at τ 2.57 (10 H), a sextet centered at τ 6.68 (2 H, J = 9.0 Hz), a quartet centered at τ 5.25 (1 H, J = 9.0 Hz), and a doublet centered at τ 4.75 (1 H, J = 8.5 Hz).

Removal of the solvent from the lower band of the thick layer plate gave 0.09 g (38%) of a yellow solid, which was subsequently identified as *trans*-benzalacetophenone by comparison with an authentic sample.

Formation of 2-Phenyl-3-benzoylthietane (2) by Selective Desulfurization of 3 with Tris(dimethylamino)phosphine.—In 25 ml of benzene was dissolved 2.86 g (0.01 mol) of 3-phenyl-4-benzoyl-1,2-dithiolane (**3**) and 1.7 g (0.011 mol) of tris(dimethylamino) phosphine. The solution was allowed to stand for 3 days at room temperature and was then evaporated to dryness under reduced pressure. The resulting residue was placed on a porous plate to remove the residual oil. Recrystallization of the solid from 95% alcohol afforded 1.5 g (60%) of 2-phenyl-3-benzoylthietane (**2**), mp 79–80°. The infrared spectrum of this material was identical in all respects with that of the product obtained from the pyrolysis of dioxide **7**. A mixture melting point was undepressed at 79–80°.

***trans*-2-Phenyl-3-benzoylthietane 1,1-Dioxide (9).**—A solution of 100 mg (0.394 mmol) of *trans*-2-phenyl-3-benzoylthietane (**2**) and 176 mg (0.804 mmol) of 80% *m*-chloroperbenzoic acid in 80 ml of methylene chloride was stirred at room temperature for 26 hr. The precipitated *m*-chlorobenzoic acid was removed by extraction with 10% sodium carbonate and then dried over magnesium sulfate. The solvent was concentrated to give a white solid, which was assigned as *trans*-2-phenyl-3-benzoylthietane 1,1-dioxide, mp 123–124°.

Anal. Calcd for $C_{16}H_{14}SO_3$: C, 67.10; H, 4.92; S, 11.19. Found: C, 66.94; H, 5.12; S, 10.92.

Pyrolysis of *trans*-2-Phenyl-3-benzoylthietane (2).—A 3-mg sample of **2** in 0.1 ml of benzene was heated to 230° in a sealed tube. After 1 hr the solution was concentrated to 0.05 ml and the residue was analyzed on a 10% FS-1265 Diatoport S column, 4 ft × 0.25 in, at 210°. The only product obtained was identified as *trans*-benzalacetophenone by comparison of retention time and infrared spectrum with those of an authentic sample.

Pyrolysis of *trans*-2-Phenyl-3-benzoylthietane 1,1-Dioxide (9).—A solid injector apparatus containing 5 mg of **9** was fitted into the injector port of an F & M gas chromatograph at 230°. After 1.5 hr the glass tube was crushed and the reaction mixture was allowed to enter a 6 ft × 0.25 in. Apeizon column at 230°. The glpc trace showed the presence of starting material (60%) and *trans*-1-phenyl-2-benzoylcyclopropane (30%). These assignments were made by comparison of retention times and infrared spectra with those of authentic samples.

Irradiation of *trans*-2-Phenyl-3-benzoylthietane 1,1-Dioxide (9).—A solution of 37 mg of 2-phenyl-3-benzoylthietane in 150 ml of cyclohexane was irradiated with an internal water-cooled mercury arc lamp (550 W) using a Pyrex filter. After 3 hr the solution was concentrated to give 29 mg of a yellow oil, which was chromatographed on a preparative thick layer plate. Elution with 5% ethyl acetate–benzene afforded only one band, which was subsequently taken up with chloroform. The chloroform extracts were distilled at 85° (0.04 mm) to give 27 mg (93%) of a mixture of *cis*- and *trans*-1-phenyl-2-benzoylcyclopropane. Gas chromatographic analysis (10% FS 1265 on Diatoport S column, 10 ft × 0.25 in., at 250°) of the oil indicated the presence of two peaks with retention times that corresponded to *cis*- (12 min) and *trans*- 1-phenyl-2-benzoylcyclopropane (14 min). Comparison of these components with authentic samples unequivocably established their identity.

Irradiation of 3-Phenyl-4-benzoyl-1,2-dithiolane (3).—2-Phenyl-3-benzoyl-1,2-dithiolane (0.200 g) in 500 ml of cyclohexane was irradiated for 5 hr using a Pyrex filter. Positive nitrogen pressure was maintained throughout the irradiation. Concentration of the solution left a yellow oil, which was chromatographed on a Florisil column. Elution of the column with 120 ml of benzene afforded 0.12 g (83%) of a pale yellow oil, whose infrared and nmr spectra indicated that it was comprised of a mixture of *cis*- and *trans*-benzalacetophenone (4:1).

Irradiation of 3-Phenyl-4-benzoyl-1,2-dithiolane 2,2-Dioxide (7).—A solution of 1.0 g of 3-phenyl-4-benzoyl-1,2-dithiolane 2,2-dioxide (**7**) in 1 l. of cyclohexane was irradiated with a 450-W Hanovia lamp using a Pyrex filter. After 3 hr the infrared spectrum showed only a trace of starting material. Concentration of the solution under reduced pressure left a pale yellow oil, which was subjected to preparative thick layer chromatography. Elution with an 8% ethyl acetate–benzene mixture afforded two bands, which were taken up in chloroform. Removal of the solvent from the lower band afforded 0.25 g (34%) of *trans*-benzalacetophenone, mp 54–56°. The upper band contained 0.22 g (30%) of a pale yellow oil, whose nmr and infrared spectra indicated it to be a mixture of *cis*- and *trans*-benzalacetophenone.

Irradiation of 2-Phenyl-3-benzoylthietane (2).—A solution of 39 mg of 2-phenyl-3-benzoylthietane in 100 ml of 95% ethanol was irradiated with a 450-W Hanovia lamp using a Pyrex filter. Aliquots were removed and analyzed by thin layer chromatography. After 3 hr the spot on a thin layer plate which was due to starting material had almost completely disappeared and a single new spot appeared in its place. Concentration of the solution left an oil which was chromatographed on a preparative thick layer plate. Elution with a 5% ethyl acetate–benzene mixture afforded a single band that was subsequently taken up in chloroform. Removal of the solvent left 27 mg (96%) of a light yellow solid, whose infrared and nmr spectra indicated it to be a mixture of *cis*- and *trans*-benzalacetophenone (4:1). Similar results were encountered when the irradiation of **2** was carried out in acetone using a Vycor filter.

Registry No.—**2**, 23852-85-9; **3**, 21551-57-5; **4**, 21551-58-6; **5**, 21551-59-7; **6**, 23853-92-1; **7**, 23877-34-1; **9**, 23852-86-0.

Acknowledgment.—We gratefully acknowledge support of this work by the National Institute of Health (Grant GM-13990-03) and the National Science Foundation (Grant GP-9385).

Stereochemistry of the Reactions of Molecular Oxygen with 1,4-Dimethylcyclohexyl and 2-Methylnorbornyl Radicals Generated from Isomeric Sources[1]

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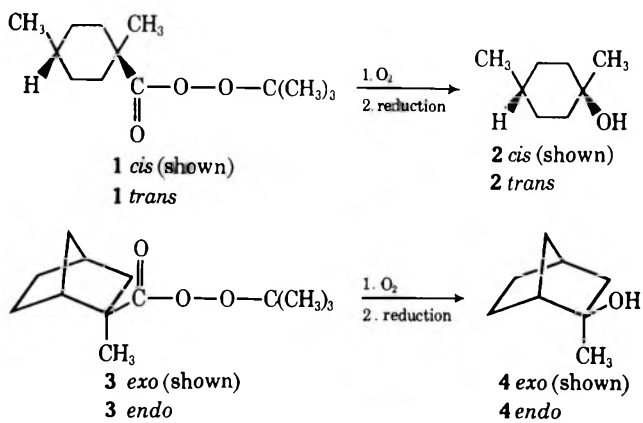
The *cis* and *trans* isomers of 1-(carbo-*t*-butylperoxy)-1,4-dimethylcyclohexane undergo thermal decomposition at 60° in cumene at essentially the same rates (*cis* isomer, $\Delta H^{\pm}$ = 27.5 kcal/mol, $\Delta S^{\pm}$ = 5.1 eu; *trans* isomer, $\Delta H^{\pm}$ = 27.8 kcal/mol, $\Delta S^{\pm}$ = 5.8 eu). The products, *cis*- and *trans*-1,4-dimethylcyclohexane, 1,4-dimethylcyclohexene, and 4-methylmethylenecyclohexane, formed from the 1,4-dimethylcyclohexyl radical are the same from both precursors. In the presence of oxygen in 1,2-dimethoxyethane or in a Freon solvent, both the *cis* and *trans* peresters gave identical yields (after reduction) of 58% *trans*- and 42% *cis*-1,4-dimethylcyclohexanol at oxygen pressures from 1 to *ca.* 600 atm. In cumene at 75°, *exo*-2-(carbo-*t*-butylperoxy)-2-methylnorbornane decomposes 6.7 times faster than its *endo* isomer ($\Delta H^{\pm}$ = 27.9 kcal/mol, $\Delta S^{\pm}$ = 6.3 eu, and $\Delta H^{\pm}$ = 30.3 kcal/mol, $\Delta S^{\pm}$ = 9.3 eu, respectively). The products resulting from 2-methyl-2-norbornyl radicals are essentially the same from either isomeric source; the same ratio of 2-methyl-2-norbornyl *exo*- and *endo*-hydroperoxides (85:15) is formed from either perester in the presence of oxygen at pressures up to *ca.* 600 atm. These results suggest that the same intermediate free radical is formed directly in a planar configuration from these isomeric perester sources. Relative rates of both decomposition and product formation are consistent with involvement of torsional effects and a planar radical center.

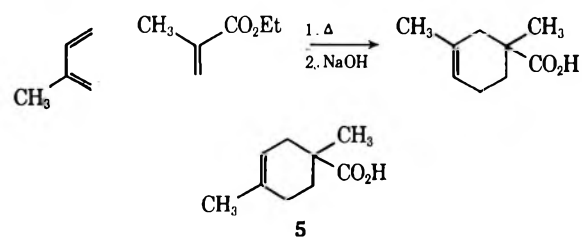
It has become well accepted that the most generally stable configuration of alkyl free radicals is planar. The most compelling data leading to this conclusion are from physical chemical measurements (esr results);[2] however, some of the chemical data (product study results) have been interpreted to indicate nonplanar configurations for intermediate radicals.[3,4] While planar configurations seem the preferred arrangement, it is also possible that most unconjugated free radicals may be initially formed in a nonplanar state. Initial radical centers may retain (for only a very short time) the tetrahedral configuration of their precursors. Physical measurements, like esr spectra, would yield no information about such metastable initial states, and stereochemical products studies would indicate nonplanar radicals only when some further reaction rapidly intercepts the initial radical. From two different isomeric sources of radicals, the products could be different if the radicals were first formed in different configurations (or conformations) and, second, if they were rapidly swept up by a trapping agent. These conditions were clearly obtained in some stereospecific reactions of isomeric 9-decalyl radicals.[5] When generated from *cis* and *trans* perester decompositions and treated quickly with the highly effective trapping agent oxygen, decalyl radicals have a "memory" of their origin which may be due to configurational differences at C-9[5a] and/or conformational differences in the rings.[5b]

To find out if such initially different radicals may also be shown to exist in other systems, we have generated 1,4-dimethylcyclohexyl radicals and 2-methylnorbornyl radicals in solution each from two different isomeric sources (**1** *cis* and *trans*, **2** *cis* and *trans*). In the presence of oxygen, hydroperoxides are formed which may be reduced to alcohols for analysis to show the existence of any stereospecific reactions. Oxygen was built up to high concentrations by use of pressures up to 600 atm.



Results

1,4-Dimethylcyclohexyl System.—The *cis*- and *trans*-1,4-dimethylcyclohexane carboxylic acids, *cis*-1-CO_2H and *trans*-1-CO_2H, required for preparations of the isomeric peresters, were prepared by Diels–Alder re-



5

action of methyl methacrylate with isoprene.[6] After hydrolysis of the esters, separation of the solid 1,4 acid from the liquid 1,3 isomer was by crystallization. Hydrogenation of the methyl ester of pure 1,4 acid **5** then gave a 62:38 mixture of *trans*-**1** and *cis*-**1** esters. This

(1) Research sponsored by the U. S. Air Force Office of Scientific Research, the Petroleum Research Fund administered by the American Chemical Society, and the National Research Council of Canada.

(2) R. W. Fessenden, *J. Phys. Chem.*, **71**, 74 (1967); M. Karplus and G. K. Fraenkel, *ibid.*, **35**, 1312 (1961); R. W. Fessenden and R. H. Schuler, *ibid.*, **39**, 2147 (1963), and references therein.

(3) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., New York, N. Y., 1966, p 30.

(4) (a) F. D. Greene, C. Chu, and J. Walia, *J. Amer. Chem. Soc.*, **84**, 2463 (1962); *J. Org. Chem.*, **29**, 1285 (1964). (b) F. G. Bordwell, P. S. Lanis, and G. S. Whitney, *ibid.*, **30**, 3764 (1965). (c) W. O. Haag and E. I. Heiba, *Tetrahedron Lett.*, 3679 (1965).

(5) (a) P. D. Bartlett, R. E. Pincock, J. H. Rolston, W. G. Schindel, and L. A. Singer, *J. Amer. Chem. Soc.*, **87**, 2590 (1965); (b) F. D. Greene and N. N. Lowry, *J. Org. Chem.*, **32**, 875 (1967).

(6) I. N. Nazkrov, A. I. Kuznetsova, and N. V. Kuznetsov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **8**, 1362 (1959); I. N. Nazkrov, A. I. Kuznetsova, and N. V. Kuznetsov, *J. Gen. Chem. USSR*, **25**, 75 (1955).

tentative assignment of *cis* and *trans* structures to these esters comes from the expectation[7] that the *trans* isomer, with a carbomethoxy group predominately in an axial (less accessible) position,[8] would have a shorter retention time on glpc analysis. Separation of these esters by preparative glpc, followed by hydrolysis, gave *trans*-1 acid, mp 46.5–47°, and *cis*-1 acid, bp 148–150 (19–21 mm). The isomeric peresters were then prepared by the reaction of the corresponding acid chlorides with the sodium salt of *t*-butyl hydroperoxide.

The stereochemical assignment of *cis* and *trans* structures, based at first on glpc retention times of esters, is supported by the nmr spectra of isomeric esters, acids, acid chlorides, and peresters. In all cases the isomer assigned to the *trans* series (axial carbonyl function) showed two broad downfield peaks at τ 7–8 not present in the spectra of the *cis* isomers. This feature apparently arises from deshielding of the axial protons at C-3 and C-5 by the C-1 carbonyl function. In addition, it is interesting to note that, just as *cis*-1,4-dimethylcyclohexane has a higher refractive index than its *trans* isomer,[9] the *cis* isomer of ester, acid chloride, and perester had the higher refractive index.

Rates of thermal decomposition of the 1,4-dimethylcyclohexyl peresters were determined in cumene solution. Variation of concentration or addition of inhibitors produced no change in the observed first-order rate constants (see Table I). Although the *cis* perester

TABLE I

RATES OF DECOMPOSITION OF 1-(CARBO-*t*-BUTYLPEROXY)-*cis*- AND -*trans*-1,4-DIMETHYLCYCLOHEXANES IN CUMENE

Perester	Temp, °C	Concn, *M*	$k_1 \times 10^5$, sec^{-1}
cis[a]	60.0	0.0441	7.52
		0.0444[c]	7.74
	70.0	0.0433	26.6
		0.0435[d]	26.6
	80.0	0.0441	84.9
		0.447	85.7
trans[b]	60.0	0.169	6.83
		0.0365	6.93
		0.0359	25.2
		0.353	25.7
		0.0417	77.9
		0.0407[d]	79.6

[a] $\Delta H^{\pm}$ = 27.5 kcal/mol, $\Delta S^{\pm}$ = 5.07 eu. [b] $\Delta H^{\pm}$ = 27.8 kcal/mol, $\Delta S^{\pm}$ = 5.75 eu. [c] Contains 0.009 *M* 2,5-di-*t*-butylhydroquinone. [d] Contains 0.10 *M* 2,6-di-*t*-butyl-4-methylphenol as inhibitor.

consistently gave a slightly greater rate constant than the *trans* isomer, the decomposition rates and activation parameters are essentially identical.

The products of decomposition of *cis* and *trans* peresters in degassed cumene at 60° were also identical within experimental error of the glpc analysis (Table II). In glyme, under 1 atm of oxygen, the products after $LiAlH_4$ reduction were *cis*- and *trans*-1,4-dimethylcyclohexanol and the two olefins, 1,4-dimethylcyclohexene and 4-methylmethylenecyclohexane. In the presence of 1 (or more) atm of oxygen pressure the intermediate free radicals are diverted from hydrogen atom transfer from the solvent and no *cis*- or *trans*-1,4-dimethylcyclohexane was formed.

TABLE II

PRODUCTS OF DECOMPOSITION OF 1-(CARBO-*t*-BUTYLPEROXY)-*cis*- AND -*trans*-1,4-DIMETHYLCYCLOHEXANES IN CUMENE AT 60°

	—Mol of product/mol of perester—	
Product	*cis*	*trans*
Carbon dioxide (by pressure)	0.96	0.90
(by weight)	0.91	0.91
t-Butyl alcohol	0.87	0.78
cis- and *trans*-1,4-dimethylcyclohexane	0.31	0.36
	(17% *cis*)	(18% *cis*)
	(83% *trans*)	(82% *trans*)
4-Methylmethylenecyclohexane	0.16	0.18
1,4-Dimethylcyclohexene	0.14	0.15

At higher than 1 atm of oxygen the solvent that was used was a 25:1 (v/v) mixture of Freon TF and glyme, respectively. This mixed solvent was chosen because of the stability of the Freon in the presence of high pressures of oxygen,[10] and the glyme served as a good source of hydrogen atoms. From this solvent the product hydroperoxides were reduced to alcohols by catalytic hydrogenation prior to analysis. The hydrogenation procedure was checked by comparing the results of hydrogenation of half of a decomposition solution with those obtained by reduction of the other half with triphenylphosphine. There was no change in the *cis*/*trans* product ratio. Also the stability of the product hydroperoxides at the temperature of the product runs was shown by putting half of a decomposition solution back in the heated bomb under oxygen for an additional 40 hr. Again there was no change in the *cis*/*trans* alcohol ratio nor in total yield of alcohol (45–60% after reduction, transfer, and concentration of the solutions before analysis). Table III summarizes the

TABLE III

PRODUCTS OF THERMAL DECOMPOSITION OF 1-(CARBO-*t*-BUTYLPEROXY)-*cis*- AND -*trans*-1,4-DIMETHYLCYCLOHEXANES IN THE PRESENCE OF OXYGEN

			1,4-Dimethylcyclohexanols	
Perester	Temp, °C	O_2 pressure, atm	% *trans*	% *cis*
trans	60 ± 0.2	1[a]	59	41
	70 ± 5	51	60[b]	40[b]
			60	40
		310	59	41
			58[c]	42[c]
	60 ± 5	610	58	42
cis	60 ± 0.2	1[a]	58	42
	60 ± 5	51	59	41
	70 ± 5	290	56	44
	60 ± 5	580	57	43

[a] In glyme, and reduced with $LiAlH_4$; all others in Freon TF–glyme (25 ml:1 ml) and hydrogenated except as noted. [b] After twice the usual decomposition time (stability check). [c] Reduced with triphenylphosphine.

(7) 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 177. For a specific example of configurational assignment by glpc to 4-methylcyclohexanecarboxylate esters, see E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Amer. Chem. Soc.*, **83**, 2351 (1961).

(8) The predominate conformations of the 1,4-dimethylcyclohexyl carbonyl compounds (**1**) are likely those with the C-4 methyl group equatorial; see the example of 1,4-dimethylcyclohexanol reported by J. J. Vebel and H. W. Goodwin, *J. Org. Chem.*, **33**, 3317 (1968). *trans*-**1** compounds would then have a predominately C-1 axial carbonyl function.

(9) See ref 7, p 172.

(10) Underwriter's Laboratories Report MH-3072, "The Comparative Life, Fire and Explosion Hazards of Freon-113," 1941; see also *Chem. Eng. News*, **43** (24), 41 (1965).

relative yields of alcohols from the 1,4-dimethylcyclohexyl peresters from various runs under different pressures of oxygen. From 1 to 610 atm, the yields of *cis* alcohol to *trans* alcohol (42% *cis*, 58% *trans*) were independent of oxygen pressure.

2-Methyl-2-norbornyl System.—The 2-methylnorbornyl peresters (*exo*-**3** and *endo*-**3**) were prepared from the known acid chlorides and sodium *t*-butyl peroxide. Good first-order decomposition of the *exo* isomer occurred in cumene, but the *endo* isomer gave an increasing rate (and some scattered points) after one or two half-lives. However, a sample of *endo* perester especially freed from traces of acid chloride gave, at high perester concentration, a good first-order kinetic plot and a rate constant the same as found at low concentrations. As shown in Table IV the *exo* isomer decomposes about seven times faster than *endo* isomer.

Table IV

Rates of Decomposition of *exo*- and *endo*-2-(Carbo-*t*-butylperoxy)-2-methylnorbornanes in Cumene

Perester	Temp, °C	Concn, M	$k_1 \times 10^5$, sec^{-1}
exo[a]	60.0	0.0333	7.78
	65.0	0.0314	14.4
	70.0	0.0340	27.5
		0.0316[c]	28.2
	75.0	0.0320	48.9
	80.0	0.0339	89.3
		0.165	90.6
endo[b]	75.0	0.0319	7.35
	80.0	0.0309	13.9
	85.0	0.0319	26.4
	90.0	0.0328	48.1
		0.159	45.9
	95.0	0.0322	84.1

[a] $\Delta H^{\ddagger}$ = 27.9 kcal/mol, $\Delta S^{\ddagger}$ = 6.31 eu. [b] $\Delta H^{\ddagger}$ = 30.3 kcal/mol, $\Delta S^{\ddagger}$ = 9.33 eu. [c] Contains 0.10 *M* 2,6-di-*t*-butyl-4-methylphenol as inhibitor.

As with the cyclohexyl peresters, the products of decomposition of isomeric norbornyl peresters in degassed cumene were the same from both sources (Table V).

Table V

Products of Decomposition of *exo*- and *endo*-2-(Carbo-*t*-butylperoxy)-2-methylnorbornanes in Cumene at 60°

Product	Mol of product/mol of perester—*exo*	*endo*
Carbon dioxide (by pressure)	0.97	1.02
(by weight)	0.96	1.00
t-Butyl alcohol	0.78	0.86
exo- and *endo*-2-methylnorbornane	0.36 (7% *exo*) (93% *endo*)	0.39 (13% *exo*) (87% *endo*)
2-Methyl-2-norbornene	0.12	0.14
2-Methylenenorbornane	0.19	0.24

The percentages of *exo*- and *endo*-2-methyl-2-norbornanols formed in the presence of various pressures of oxygen are given in Table VI. After reduction of the product solutions by hydrogenation the 2-methyl-2-norbornanols were the only products analyzed, although numerous other unidentified peaks appeared in the glpc tracings. Many of these compounds undoubtedly arise from oxidation of the solvent. The yields of alcohols were only 15–25%; however, their ratio was found to be independent of oxygen pressure and was the same from either *exo* or *endo* perester (85:15 with *endo*-2-methyl-2-norbornanol, *i.e.*, *exo* OH group, the major isomer).

Table VI

Products[a] of Thermal Decomposition of *exo*- and *endo*-2-(Carbo-*t*-butylperoxy)-2-methylnorbornanes in the Presence of Oxygen

Perester	Temp, °C	O_2 pressure, atm	2-Methyl-2-norbornanols—% *endo*-methyl	% *exo*-methyl
exo	65 ± 0.2	1[b]	85[c]	15
	60 ± 0.5	280	85[c]	15
			85	15
	70 ± 5	600	84	16
endo	65 ± 0.2	1[b]	85	15
	60 ± 0.5	270	86	14
			87[c]	13
	70 ± 0.5	560	84	16

[a] After hydrogenation. [b] In glyme; all other runs in Freon TF (25 ml)–glyme (1 ml). [c] Analyzed before concentration by distillation of the solvent.

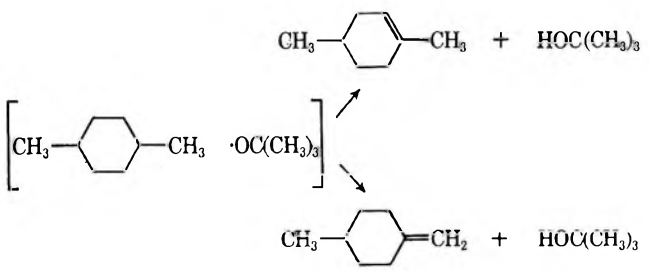
Discussion

The high yields of CO_2 and the absence of carbonyl-containing products from the four peresters studied here indicated that the formation of alkyl radical, CO_2, and *t*-butoxy radical occurs directly (in one step) from the peresters. For formation of tertiary free radicals from peresters this is the expected mechanism,[11] and the rates and activation parameters of the peresters are similar to those of known peresters decomposing by such a concerted path. It is the structure of the initial radical that is the question of special interest here. Lorenz, Rüchardt, and Schacht[12] have presented kinetic studies of cycloalkyl peresters which suggest that, at the transition state for decomposition, the radical sites remain nonplanar. As it is also known that there is relatively little preference for planarity in free alkyl radicals,[13] there could be an initial state after the transition state in which the radical remains in a nonplanar configuration. With 9-decalyl radicals the conversion of a nonplanar radical center to a planar state can occur only with concomitant movement of part of the ring system in a manner similar to a chair–chair interconversion.[5a] Any questions concerning possible restraints on a pure configurational change of the radical center were blurred out by the requirements for this conformational change. With the isomeric 2-methylnorbornyl and 1,4-dimethylcyclohexyl radical sources (**1** and **3**) no complex conformational changes are necessary to produce a planar radical center; a methyl group need only move into a plane with other atoms attached to the radical center. Although an extremely efficient radical trap at high pressures was used in our attempt to intercept this movement, it is perhaps surprising to few that no stereospecific trapping was obtained. Since oxygen trapping did not succeed in demonstrating a "memory" of origin on the part of these alkyl radicals, it seems unlikely that any external trapping agent would be able to do so.

(11) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).
(12) P. Lorenz, C. Rüchardt, and E. Schacht, *Tetrahedron Lett.*, 2787 (1969).
(13) *Cf.* L. F. Humphrey, B. Hodgson, and R. E. Pincock, *Can. J. Chem.*, **46**, 3099 (1968), and references therein.

9-Decalyl radicals therefore remain unique as a case in which isomeric initial cyclohexyl radicals have been proven. It seems this difference is not due to any innate hesitancy on the part of initial radical centers in becoming planar, but is due to a lag in obtaining a conformationally more stable state in the cyclic ring system. Indeed, it has been suggested that the decalyl radical center may be formed in a planar state from both *cis* and *trans* peresters even though conformational differences in the rings still remain.[5b] In this regard, evidence for two conformationally different 9-decalyl cations, both with planarity at the 9 atom, has recently been presented.[14]

Stereospecific trapping of isomeric radicals by an *internal* agent (*i.e.*, reaction of geminate caged radicals) may account for formation of different products from isomeric radical sources.[15] With 1,4-dimethylcyclohexyl radical reacting with *t*-butoxy radical as a caged pair, the same ratio of olefins is formed from either *cis* or *trans* source. If the newly formed radicals retain



any individual structural features similar to the original peresters, this individualism does not last even long enough to give different products within the cage. As movement of only a methyl group is sufficient to make the radicals planar, it is probable that radicals from isomeric sources are made identical, if not at the transition state, immediately thereafter.

A movement of the groups of the 2-methylnorbornyl peresters during the development of the transition states is consistent with their relative rates of decomposition. For the *endo* compound, Schleyer's[16] suggestion of a destabilizing torsional effect as the *exo* methyl group sweeps past the bridgehead hydrogen atom may account for the slower rate of reaction of this isomer. The *exo* perester reacts faster as the movement of the 2-methyl (*endo*) group does not eclipse it with the bridgehead C–H bond.[17]

The products of reaction of the radicals can also be rationalized on the basis of a torsional effect. In the reaction of cyclohexyl radicals, a favoring of axial attack on R· (planar) would be expected to promote formation of *trans* product.[18] For hydrogen atom transfer, 83% *trans* and 17% *cis* 1,4-dimethylcyclohexane was formed. As expected,[18a] the less selective reagent oxygen gave a more statistical 58% *trans* and 42% *cis* product. In the norbornyl case the greater torsional effects present would strongly favor *exo* attack of reagent;[16] the percentage found for H transfer from cumene was 94% *exo* approach yielding *endo*-2-methylnorbornane (Table V), and, for reaction with oxygen, 85% *exo* attack yielding 2-methyl-*exo*-2-norbornanol (Table VI).

In summary, the radicals from the tertiary peresters studied here are probably formed directly in a planar state and these give nonstereospecific products. The restraints present in more complicated cyclic systems (which give rise to memory effects in 9-decalyl radicals) seem to be just barely sufficient to give stereospecific trapping by a highly reactive external reagent. It seems that a relatively slow conformation change of the ring system accounts for the existance of two very short-lived decalyl radicals. Whether such a property can be attained by some complex acyclic system remains to be seen, but it is clear that restraints more incumbering than the movement of a simple methyl group must be present.

Experimental Section[19]

Materials.—Cumene was stirred with concentrated sulfuric acid, then refluxed over sodium for 24 hr, and distilled through a Vigreux column, taking a center cut with bp 152–152.2° at 761 mm. Freon TF (1,1,2-trichloro-1,2,2-trifluoroethane) was supplied by Du Pont and used without further purification, or stirred over and distilled from magnesium sulfate, bp 47.4–47.5° at 757 mm. Glyme (1,2-dimethoxyethane) was refluxed over and distilled from sodium through a Vigreux column. The distillate was treated with lithium aluminum hydride and distilled, bp 85° at 756 mm. Petroleum ether (bp 30–60°) was treated with concentrated sulfuric acid and then distilled from sodium. Fractions with several different boiling points were used.

1,4-Dimethyl-3-cyclohexene-1-carboxylic Acid (5).—The distilled product (258 g) from the Diels–Alder reaction[6] of isoprene and methyl methacrylate was refluxed for 1.5 hr with 340 ml of 40% aqueous sodium hydroxide. The solution was cooled and acidified with 360 ml of 12 *N* hydrochloric acid; the product was extracted into ether. The ether solution was dried and evaporated and the residual oil was cooled to 5° to crystallize. After filtration and recrystallization from methanol–water at about −5°, the yield of white crystals, mp 64.5–66° (lit.[6] mp 62–63°), was 73.0 g. Analysis by glpc of the methyl ester (from ethereal diazomethane) showed that the 1,3-dimethyl isomer was absent.

Separation of 1-Carbomethoxy-*cis*- and -*trans*-1,4-dimethylcyclohexanes.—1-Carbomethoxy-1,4-dimethylcyclohex-3-ene (30.8 g) from the corresponding acid plus ethereal diazomethane was hydrogenated at room temperature and pressure in 100 ml of 95% ethanol using 3.0 g of 10% palladium on charcoal as catalyst. Hydrogen consumption ceased at the theoretical value. Analysis by glpc, after filtration and evaporation of the ethanol, indicated 62% *trans* ester (1-CO_2CH_3) and 38% *cis* ester (1-CO_2CH_3). No unsaturated starting material was detected by glpc.

The *cis* and *trans* esters were separated by preparative-scale glpc (500-μl samples) on a Model A-700 "Autoprep" fitted with a 10-ft Carbowax 20M on 60–80 mesh Chromosorb W column at 150° and a flow rate of 63 cc/min. The *cis* and *trans* isomers were separated by 10–11 min under these conditions. Collection was 80% efficient, and 20.3 g of *trans* ester ($n^{20}D$ 1.4405) and 13.7 g of *cis* ester ($n^{20}D$ 1.4459) were obtained. Efficiency of the separation was checked by reinjection on a 6-ft TCEP or 10-ft Carbowax 20M column, and both isomers were found to be >99% pure. These glpc-collected samples were used without further purification.

(14) A. F. Boschung, M. Grisel, and C. A. Grob, *Tetrahedron Lett.*, 5169 (1968). See also R. E. Hornish, G. Liang, and R. C. Fort, Jr., Abstracts, the 158th National Meeting American Chemical Society, New York, N. Y., Sept 1969, ORGN-2.

(15) *Cf.* E. M. Kosower, "An Introduction to Physical Organic Chemistry," Johns Wiley & Sons, Inc., New York, N. Y., 1968, p 352–359; E. I. Heiba and R. M. Dessau, *J. Amer. Chem. Soc.*, **89**, 2238 (1967); H. M. Walborsky and C. Chen, *ibid.*, **89**, 5499 (1967); M. J. S. Dewar and J. M. Harris, *ibid.*, **91**, 3653 (1969).

(16) P. von R. Schleyer, *ibid.*, **89**, 699, 701 (1967).

(17) Decompositions of peroxy compounds leading to norbornyl radicals have relative *exo/endo* rates of *ca.* 4–10; (a) P. D. Bartlett and R. E. Pincock, *ibid.*, **84**, 2445 (1962); (b) H. Hart and F. J. Chloupek, *ibid.*, **85**, 1155 (1963); (c) P. D. Bartlett and J. M. McBride, *ibid.*, **87**, 1727 (1965).

(18) See for example (a) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *ibid.*, **90**, 5793 (1968); (b) C. L. Osborn, T. V. Van Auken, and D. J. Trecker, *ibid.*, **90**, 5806 (1968).

(19) Further details can be obtained from the Ph.D. Thesis of W. Schindel, University of British Columbia, 1968, available on microfilm through the National Library of Canada, Ottawa.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found (*cis* isomer): C, 70.29; H, 10.74. Found (*trans* isomer): C, 71.00; H, 11.03.

***trans*-1,4-Dimethylcyclohexanecarboxylic Acid.**—1-Carbomethoxy-*trans*-1,4-dimethylcyclohexane (15.0 g) was heated and stirred for 21 hr with 45 ml of 40% aqueous sodium hydroxide to which had been added 6 ml of ethanol. The precipitated salt was collected by filtration, washed with ether, and dissolved in hot water and the carboxylic acid was generated with concentrated hydrochloric acid. The white solid (13.5 g) was recrystallized from methanol–water (recovery of 88%), mp 46.5–47°.

***cis*-1,4-Dimethylcyclohexanecarboxylic Acid.**—The *cis* acid was prepared by refluxing 8.0 g of 1-carbomethoxy-*cis*-1,4-dimethylcyclohexane with 25 ml of 40% aqueous sodium hydroxide and 3.0 ml of ethanol for 4 hr. After acidification and extraction the product was distilled, bp 148–150° at 19–21 mm, with 85% yield. Koch and Haaf[20] reported synthesizing both 1,4-dimethylcyclohexanecarboxylic acids (mp 35° for one isomer, bp 143° (20 mm) for the other), but did not specify which isomer was *cis* and which was *trans*.

***trans*-1,4-Dimethylcyclohexanecarbonyl Chloride.**—Reaction of 10 g of *trans* acid with 30 ml of thionyl chloride at room temperature for 15 hr, followed by 2 hr of refluxing, yielded 9.8 g (88%) of colorless liquid, bp 88–89° (14 mm) or 30.5–31° (1.3–1.5 mm), n^{20}D 1.4605.

Anal. Calcd for $C_9H_{15}ClO$: C, 61.89; H, 8.66; Cl, 20.29. Found: C, 61.99; H, 8.53; Cl, 20.50.

***cis*-1,4-Dimethylcyclohexanecarbonyl Chloride.**—*cis*-1,4-Dimethylcyclohexanecarboxylic acid (10.0 g) with thionyl chloride, as with the *trans* isomer above, gave the corresponding acid chloride, bp 89.5–90° (12.5 mm). The yield was 10.4 g (93%), n^{22}D 1.4673 or $n^{22.5}$D 1.4670.

Anal. Calcd for $C_9H_{15}ClO$: C, 61.89; H, 8.66; Cl, 20.29. Found: C, 61.95; H, 8.41; Cl, 20.63.

1-(Carbo-*t*-butylperoxy)-*trans*-1,4-dimethylcyclohexane (**1**).—To a stirred suspension of 4.0 g of sodium *t*-butylperoxide in 50 ml of anhydrous ether at 0° was added dropwise over 20 min 5.0 g of *trans*-1,4-dimethylcyclohexanecarbonyl chloride in 10 ml of dry ether. After stirring for 4 hr at 0°, 20 ml of distilled water was added and stirring was continued for 15 min. Then 50 ml of purified petroleum ether (30–60°) was added, the water layer was separated off, and the organic phase was washed with two 10-ml portions of cold 10% sulfuric acid, five 10-ml portions of 10% sodium carbonate, five 10-ml portions of distilled water, and one 20-ml portion of brine. The solvent was removed by rotary evaporation at about 15–20°, and the resulting oil taken up in 50 ml of purified petroleum ether (40–41°) and washed well with distilled water and once with brine to remove the *t*-butyl hydroperoxide present. Drying over magnesium sulfate, followed by thorough rotary evaporation, gave 5.30 g (81%) of a clear, colorless oil with $n^{20.5}$D 1.4470.

Anal. Calcd for $C_{13}N_{24}O_3$: C, 68.38; H, 10.59. Found: C, 67.93; H, 10.46.

1-(Carbo-*t*-butylperoxy)-*cis*-1,4-dimethylcyclohexane (**1**).—This perester was prepared from 5.0 g of the corresponding *cis* acid chloride (XVI) and 4.1 g of sodium *t*-butylperoxide in a manner analogous to the *trans* isomer. The yield was 5.5 g (84%) of very pale yellow liquid with $n^{20.5}$D 1.4501. A second preparation gave n^{20}D 1.4496.

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.56; H, 10.47.

The above are typical preparations, and more perester was prepared in a similar fashion when needed. One preparation of the *cis* perester showed a weak to medium peak at 1810 cm^{-1} in the ir spectrum (possibly anhydride). Some preparations indicated unreacted acid chloride was present (infrared spectrum), and this was removed by putting the perester back to stir with more sodium salt. The peresters were stored at −10 to −15°. Neither compound crystallized.

***exo*- and *endo*-2-methyl-5-norbornene-2-carboxylic acids** were separated by the iodolactonization procedure of Rondestvedt and Ver Nooy.[21] Hydrogenations then gave the *exo* acid (**3**), mp 51.3–52° (lit. mp 50.5–51.6°,[22] 52–53°[23]), and the *endo* acid (**3**) mp 96.0–96.2° (lit. mp 92–93°,[23] 97.5–98.5°).[24] The observed and reported nmr spectra were in agreement, and the methyl esters (from etheral diazomethane) of our samples showed the absence of isomeric impurities. The acid chlorides were prepared by reaction of the acids with thionyl chloride.

***exo*-2-(Carbo-*t*-butylperoxy)-2-methylnorbornane** (*exo*-**3**).—A stirred suspension of 2.5 g of sodium *t*-butyl peroxide in 40 ml of anhydrous ether was cooled to 0°. Over a 15-min period, 3.5 of 2-methylnorbornane-2-*exo*-carbonyl chloride in 10 ml of dry ether was then added from a dropping funnel. Half an hour later, 0.5 g of sodium *t*-butyl peroxide was added, and finally, after 3 hr, another 0.2 g of sodium salt was added. After a total time of 4 hr at 0° the reaction mixture was filtered; the salts and paper filter were washed well with dry ether. The ether solution was then extracted with one 10-ml portion of water, two 10-ml portions of 10% sulfuric acid, four 10-ml portions of 10% sodium carbonate, two 10-ml portions of distilled water, and one 10-ml portion of brine, dried over magnesium sulfate, and rotary evaporated at ~20° to yield 4.32 g of liquid containing *t*-butyl hydroperoxide (as shown by the infrared spectrum). This crude product was taken up into 50 ml of pentane, washed 10 times with 10-ml portions of distilled water, and dried over magnesium sulfate, and the solvent was rotary evaporated as above. The last traces of solvent were removed by pumping down to 1–3 mm at room temperature for a short time. The colorless oil (3.77 g, 82%) had $n^{19.5}$D 1.4674. A second preparation gave perester with $n^{19.5}$D 1.4675 in 87% yield.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.15; H, 9.75.

***endo*-2-(Carbo-*t*-butylperoxy)-2-methylnorbornane** (*endo*-**3**).—The preparation of the *endo* perester from the acid chloride was identical with that of the *exo* perester. The yield was 4.14 g (90%) of clear, colorless perester, $n^{19.5}$D 1.4652. Perester, with $n^{19.5}$D 1.4650, was obtained in 88% yield from a second preparation.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.09; H, 9.76.

Authentic samples of the alcohols *cis*- and *trans*-**2** and *exo*- and *endo*-**4**, and various olefins were prepared for glpc comparison with product solutions. Addition of methylmagnesium iodide to 4-methylcyclohexanone gave 46% *trans* alcohol **2**, mp 71.5–72° (lit.[25] 72.5°), and 54% *cis* alcohol **2**, a liquid at room temperature (lit.[25] mp 24°). Pure samples of each isomer were obtained by glpc. 1,4-Dimethylcyclohexane was prepared by action of phosphorous oxychloride in pyridine on *cis* and *trans* alcohol **2**. 4-Methylmethylenecyclohexane was prepared by the procedure of Greenwald, *et al.*,[26] and obtained pure by glpc. *cis*- and *trans*-1,4-dimethylcyclohexanes were separated from a commercial mixture by glpc and identified by refractive indices.

2-Methyl-*endo*-2-norbornanol (*endo*-**4**), mp 31.5–33.0° (lit.[27] mp 32.5–32°), was obtained by Grignard reaction with norcamphor. The isomer (*exo*-**4**), mp 80–80.7 (lit. mp 82–82°), was obtained by the procedure of Brown.[28] 2-Methyl-2-norbornene and 2-methylenenorbornane, prepared by dehydration of **4**, were separated by glpc and identified by their nmr and infrared spectra. A mixture of 84% *endo*- and 16% *exo*-2-methylnorbornane was prepared by hydrogenation of the mixture of olefins obtained by dehydration of 2-methyl-2-norbornanol.

Kinetic studies[19] were carried out by infrared analysis of individual sealed samples as previously described.[29] A Perkin-Elmer Model 137-B spectrophotometer was used with matched 0.523-mm sodium chloride cells.

Product studies[19] in degassed cumene were carried out as previously described.[29]

Product Studies at High Oxygen Pressures.—The general procedure was as follows. The desired perester, 0.50 g, was dissolved in 25 ml of Freon TF, 1 ml of glyme was added, and the solution was placed in the glass liner of a steel, high-pressure

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bomb (50 ml in volume) supplied by the Parr Instrument Co. The apparatus was flushed several times with oxygen, and oxygen was then introduced into the bomb at the desired pressure, making a rough allowance for the increase in pressure on raising the temperature. The bomb was then heated, without agitation, to 60 or 70° by means of a custom-made heating mantle for the desired length of time, measuring the temperature (±5°) by a thermocouple. The pressure fluctuated somewhat (±5–15%), especially at the higher pressures, and values reported are "averages." The bomb was then allowed to cool to room temperature before slowly releasing the oxygen. Because of possible explosions, strict safety precautions (special explosion-proof rooms, remote control of the bomb at all times, etc.) and proper equipment are mandatory.

The products from decompositions using Freon TF were reduced by hydrogenation. In a typical reduction, the solution from the decomposition was transferred, along with ether or Freon TF washings, from the bomb to the glass bottle of a Parr hydrogenator. Catalyst, 0.50 g of 10% palladium on charcoal, was added, and hydrogenation carried out for about 1.5 hr at ambient temperature and an initial hydrogen pressure of approximately 50 psi. The catalyst was removed by filtration, and the solution concentrated by distillation at atmospheric pressure through a 4–4.5-cm column (packed length) filled with perforated stainless steel plates, followed by pumping down twice to *ca.* 180 mm on a rotary evaporator. Concentration was necessary since the solvent interfered with glpc analysis on the standard 0.25-in.-diameter columns when large samples (necessitated by the dilute nature of the solution) were injected. Products were not fractionated by this concentration procedure as shown by the consistency of the results in various runs.

Solutions were analyzed by glpc using Varian–Aerograph A-90-P and Perkin-Elmer Model 226 gas chromatographs. Products were identified by peak enhancement on addition of authentic compounds. Yields were obtained by comparison of peak areas with those obtained from standard samples. Separation of *exo* and *endo* alcohols **4** was by use of a 150 ft × 0.01 in. (i.d.) Quadrol capillary column. Other separations were accomplished by various standard columns.[19]

Registry No.—1,4-Dimethylcyclohexyl radical, 24151-68-6; 2-methylnorbornyl radical, 24212-34-8; *trans*-1,4-dimethylcyclohexanecarboxylic acid, 24097-70-9; *cis*-1,4-dimethylcyclohexanecarboxylic acid, 24097-71-0; *trans*-1,4-dimethylcyclohexanecarbonyl chloride, 24097-72-1; *cis*-1,4-dimethylcyclohexanecarbonyl chloride, 24097-73-2; *cis*-**1**, 24097-65-2; *trans*-**1**, 24097-66-3; *cis*-1-CO_2CH_3, 23250-42-2; *trans*-1-CO_2CH_3, 23059-38-3; *exo*-**3**, 24162-40-1; *endo*-**3**, 24097-69-6.

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Kinetics of the Reverse Diels–Alder Dissociation of Substituted Dicyclopentadienes

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The kinetics of the dissociation of dicyclopentadienes substituted with alkyl and ester groups were measured. The effects of these groups on the kinetics of the dissociation are described. The dimer of *t*-butylcyclopentadiene was prepared and found to be 1,4-di-*t*-butyltricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene.

Although kinetics of the dissociation of dicyclopentadiene have been the subject of a number of studies,[2] there is very little information in the literature on the dissociations of substituted dicyclopentadienes. In a previous communication from this laboratory,[3] the kinetics of the dissociation of dicyclopentadiene (**1**) and the methyl esters of dicyclopentadienemonocarboxylic acid (4-carbomethoxytricyclo[5.2.1.$0^{2,6}$]-deca-3,8-diene, **2**) and dicyclopentadienedicarboxylic acid (4,9-dicarbomethoxytricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene, **3**) were reported.

Reactive dienophile trapping agents removed the monomer as it was formed and allowed measurement of the dissociation reaction without interference from the dimerization reaction. These dissociations followed first-order kinetics with respect to the dimer[4] and were independent of the nature or concentration of the trapping agent.[3]

The previous kinetic measurements had been made by a novel and rapid technique using a differential scanning calorimeter,[3] and this technique was extended to other substituted cyclopentadiene dimers which were available. This communication reports the results of these measurements.

Results

The kinetics of the dissociation reactions were measured with the differential scanning calorimeter, which measures directly the rate of absorption or evolution of heat in the sample as its temperature is being raised at a controlled rate. Liquid samples, such as the solution samples used in the present work, are in a layer of 1 mm or less thickness and are in good thermal contact with the heating and temperature sensing elements of the instrument. Problems of thermal gradients within the samples are therefore largely eliminated in these measurements.

Since the samples are in the form of solutions of reagents, such as are used in more conventional kinetic measurements, the recent criticisms[5] of the use of thermoanalytical methods to obtain kinetic data do not apply to the present measurements.

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

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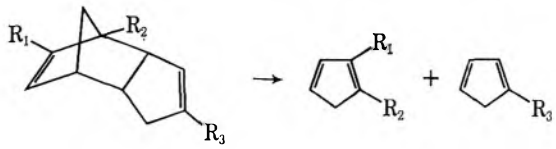
TABLE I

DISSOCIATION OF DICYCLOPENTADIENES

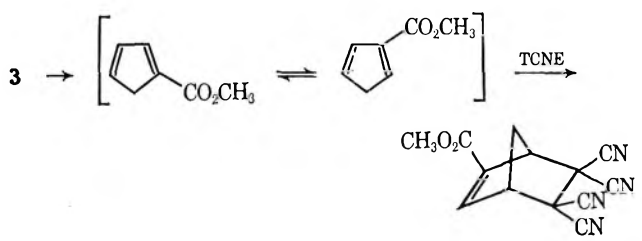


Compound	R_1	R_2	R_3	Trapping agent[a]	E_a, kcal/mol	Log A	ΔS^*, gibbs/mol
1	H	H	H	A	35.1	13.7	1.1
2	H	H	CO_2CH_3	A	32.2	13.5	0.7
3	CO_2CH_3	H	CO_2CH_3	A	30.5	13.1	1.5
				B	30.0	13.3	0.5
				C	30.8	13.1	1.4
4	$CO_2C_6H_5$	H	$CO_2C_6H_5$	C	29.4	12.8	2.9
5	CH_3, H		CH_3	C	37.1	14.4	4.3
6	H	t-C_4H_9	t-C_4H_9	B	27.0	12.5	−3.9
				D	27.2	12.7	−3.1

[a] Trapping agents: A, N-phenylmaleimide in tetraglyme; B, tetracyanoethylene in tetraglyme; C, dibutyl maleate, no solvent; D, evaporation of monomer from open capsule.

The results of the kinetic measurements of the reverse Diels–Alder dissociation of the substituted dicyclopentadienes are given in Table I. The Arrhenius parameters are averages from five or more independent runs for each reaction. The standard deviations were 3% or less of the values for the parameters.

The kinetic parameters found for the dissociation of dicyclopentadiene **1** are quite close to those reported by Khambata and Wasserman[6] for the dissociation of dicyclopentadiene as the pure liquid, E_a = 35.3 kcal/mol, log A = 13.6. The dissociation of the dimethyl ester of dicyclopentadienedicarboxylic acid **3** was measured in the presence of three dienophilic trapping agents. The Arrhenius parameters for these reactions were identical within experimental error, thus indicating that the dissociation of the dicyclopentadiene derivative is the rate-determining step and that the rate of the reaction is independent of the trapping agent. The dissociation is followed by the rapid interconversion between 1- and 2-carbomethoxycyclopentadiene and the reaction of one or both of these isomers with the trapping agent.[4]



t-Butylcyclopentadiene was prepared as the equilibrium mixture of the 1 and 2 isomers to provide a cyclopentadiene holding a bulky substituent group which should decrease the stability of the dimer. The t-butylcyclopentadiene showed no evidence of dimerization by gas chromatography after long standing at 0°, but dimerized fairly rapidly at 120°. The nmr spectrum of the dimer showed two vinyl protons as a doublet at τ 4.15 and one vinyl proton as a characteristic "quartet" at τ 4.10. These features had been found earlier[4] to be typical of 1,4 substitution in the dicyclopentadiene ring system. By analogy with the "liquid dimer" from methyl cyclopentadienecarboxylate,[4] the dimer of t-butylcyclopentadiene is therefore assigned the structure of *endo*-1,4-di-t-butyltricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene (**6**). The evidence does not exclude the possibility of the 4,7-di-t-butyl isomer.

The dimethyldicyclopentadiene was the commercially available "methyl cyclopentadiene dimer." The nmr spectrum of this dimer showed a ratio of vinyl to aliphatic protons of 1:5.8, which corresponds to an approximately equimolar mixture of 1,4- and 4,9-dimethyltricyclo[5.2.1.$0^{2,6}$]deca-3,8-dienes (**5**). Gas chromatography showed also that the dimer was a mixture of two compounds in approximately equal amounts. A similar mixture of dicyclopentadienedicarboxylic acids was previously found[4] from the low-temperature carbonation of cyclopentadienyl sodium.

The data in Table I show the effects of the type of substitution on the rates of dissociation of the substituted dicyclopentadienes. The entropies of activation are quite close to zero, as has been found in other reverse Diels–Alder reactions.[2]

The energies of activation show both electronic and steric effects of the substituents on the reactions. The first three reactions show the effects of successive substitutions with electron-attracting carbomethoxy groups, where each group decreases the energy of activation by about 2.5 kcal. When the methoxy groups are changed to phenoxy groups, a further slight decrease in activation energy occurs, probably as a result of increased strain on the dicyclopentadiene ring system from the proximity of the two large phenyl groups.

The large activation energy for the dissociation of methyl cyclopentadiene dimer would seem to indicate that the electron-releasing methyl groups tend to hinder the dissociation of the dicyclopentadiene ring system. Although this dimer is a mixture of at least two isomers, the Arrhenius plots for the dissociation were linear over the 40° temperature range of the plots. If there had been substantial differences between the rates of dissociation of the isomers, the

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Arrhenius plots would not have been linear at each of the scan rates used for the measurements.

The kinetic parameters for the dissociation are calculated from the rate of evolution of heat as the reaction proceeds. The quantity of heat evolved by the reaction is the sum of the heats from the slow, endothermic dissociation of the dimer and the fast, exothermic reaction of the monomer with the trapping agent. When the dimer of *t*-butylcyclopentadiene was heated in the presence of N-phenylmaleimide or dibutyl maleate, the heats of the endothermic and exothermic steps were nearly equal. Thus, the heats of the reactions were too small to provide the bases for kinetic measurements. When tetracyanoethylene was used as the trapping agent, as illustrated above in the equation with compound **3**, a small, but measurable, heat of reaction was observed. This was used to calculate the kinetics of the dissociation of the dimer of *t*-butylcyclopentadiene. These kinetic parameters were confirmed by measuring the rate of evaporation as the dimer dissociated to the volatile monomer in open sample capsules in the differential scanning calorimeter.

It was originally assumed that the large *t*-butyl groups would interfere with each other and facilitate the dissociation of the dimer of *t*-butylcyclopentadiene. It was found, however, that the only major product of the dimerization of *t*-butylcyclopentadiene was the 1,4-di-*t*-butyl isomer **6** (see above), in contrast to the dimerization of methyl cyclopentadienecarboxylate, where the 4,9-dicarbomethoxy isomer is the major product.[7] Molecular models of the dimer show that the *t*-butyl groups are well separated from each other, and would not be expected to facilitate the dissociation. By analogy with the dissociation of methylcyclopentadiene dimer, it would seem that the electron-releasing *t*-butyl groups would retard the dissociation of the dimer. It was found, however, that the energy of activation of this dissociation is the lowest value in Table I. There is no readily obvious way to reconcile the low energy of activation for the dissociation of the dimer of *t*-butylcyclopentadiene with the spectral evidence for its structure.

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Experimental Section

Sources of Reagents.—Dicyclopentadiene (practical grade, 95%), tetracyanoethylene, and N-phenylmaleimide were recrystallized to constant melting point before use. Reagent grade dibutyl maleate was used without further purification. Tetraglyme was purified by vacuum distillation from calcium hydride [bp 105° (0.5 mm)]. The preparations of 4-carbomethoxytricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene, 4,9-dicarbomethoxytricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene, and 4,9-dicarbophenoxytricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene have been described previously.[4] Methylcyclopentadiene dimer was used as obtained from Aldrich Chemical Co.[8]

t-Butylcyclopentadiene was prepared as the equilibrium mixture of the 1 and 2 isomers from cyclopentadienyl sodium and *t*-butyl bromide by the method of Riemschneider.[9] The dimer of *t*-butylcyclopentadiene was prepared by heating the monomer at 120° for 7 hr under a stream of nitrogen, and then removing the small amount of unreacted monomer *in vacuo*. The solid dimer was recrystallized from methanol to give 1,4-di-*t*-butyltricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene (**6**): mp 65–66° (lit.[10] mp 69°); nmr τ 4.1 (d, 2 H), 4.9 ("quartet," 1 H), 9.1–9.2 (2 s, 18 H).

Kinetic Measurements.—All kinetic measurements were made with the Perkin-Elmer DSC-1 differential scanning calorimeter.[8] The measurements were made on 10–20-μl samples of solutions of the dimer, trapping agent, and solvent or excess liquid trapping agent contained in sealed aluminum capsules. The technique and calculations of the kinetic parameters have been described previously.[3] The calculations were carried out on a Control Data Corp. 1700 digital computer. The Arrhenius parameters were calculated from rate constants over 40–80° ranges between 390° and 525°K, depending on the scan rates and the values of the kinetic parameters. Each set of kinetic parameters recorded is the average from five or more independent runs at two or more scan rates. The standard deviations for the kinetic parameters were 3.5% of the values or less.

Registry No.—**1**, 77-73-6; **2**, 22388-06-3; **3**, 23163-00-0; **4**, 24164-80-5; **5**, 7570-08-3; **6**, 24165-37-5.

Acknowledgment.—The author wishes to express his thanks to Dr. S. P. Rowland for his helpful discussions, to Mr. Emory E. Coll for his valuable assistance with the computer, and to Mr. Gordon J. Boudreaux for his assistance with the nmr spectra.

(8) Mention of a company and/or product by the U. S. Department of Agriculture does not imply approval or recommendation of the company or product to the exclusion of others which may also be suitable.

(9) R. Riemschneider, A. Reisch, and H. Horak, *Monatsh. Chem.*, **91**, 805 (1959).

(10) R. Riemschneider and R. Nehring, *ibid.*, **90**, 568 (1959).

Oxidation of Alkyl Aromatic Hydrocarbons by Potassium 12-Tungstocobaltate(III)[1]

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The oxidation of alkyl aromatic hydrocarbons by the heteropoly compound $K_5[Co^{III}O_4W_{12}O_{36}]\cdot H_2O$ was examined in order to determine whether inner- or outer-sphere electron transfer occurs when aromatic radical cations are formed during oxidations by metal ions. The oxidations were conducted at 96° in a heterogeneous system composed of solid $K_5[Co^{III}O_4W_{12}O_{36}]\cdot H_2O$ and the pure hydrocarbon (toluene and *o*-, *m*-, and *p*-xylene). The oxidation products were diphenylmethane derivatives, demonstrating the intermediate formation of benzyl carbonium ions. The oxidation of toluene in the presence of excess benzene produced diphenylmethane. The proposed mechanism consists of radical cation formation *via* outer-sphere oxidation in which the electron is removed from the aromatic π system and conducted through the tungstate framework to the Co^{III} ion. The radical cation expels a proton and the resulting benzyl radical is similarly oxidized to the carbonium ion. In aqueous acetic acid a similar mechanism appears to hold.

Recent reports[2,3] have shown that the oxidation of alkyl aromatic hydrocarbons by cobalt(III) acetate and a species identified[4] as the hexachlorocobaltate(III) anion proceed *via* intermediate formation of aromatic radical cations. The electron transfer has been characterized as occurring *via* an electrophilic interaction,[2] but the details of this interaction, *i.e.*, whether the electron transfer is the result of an inner- or outer-sphere process, could not be determined. It was desirable, therefore, to seek metal oxidants, capable of aromatic radical cation production, with which the electron-transfer mechanism could be more clearly defined.

Gillard[5] has recently shown that the excited triplet states of octahedral Co^{III} are better oxidants than the singlet ground states, but prior excitation to the excited states is necessary before reduction could occur. Tetrahedral Co^{III}, with a ground-state configuration $e^3t_2^3$ (^5E), is easily reduced without excitation by electron transfer to the low-energy e orbital, resulting in the configuration $e^4t_2^3$ ($^4A_2$), the ground state of tetrahedral Co^{III}. Tetrahedral Co^{III} has been observed in yttrium garnets,[6] but is of little interest for chemical reactions in this form. The only other known occurrence is in yellow potassium 12-tungstocobaltate(III),[7-10] $K_5[Co^{III}O_4W_{12}O_{36}]$, which is of more interest as an oxidant for aromatic hydrocarbons.

Heteropoly ion chemistry has been reviewed.[11,12] Crystalline $K_5[Co^{III}O_4W_{12}O_{36}]\cdot 20H_2O$ has the "Keggin" structure with tetrahedral Co^{III};[13-15] the Co^{II} form is isomorphous.[14] Electron exchange between the Co^{II} and Co^{III} compounds in solution is relatively rapid and proceeds *via* an outer-sphere electron transfer[16] unaccompanied by atom transfer.[17] Such electron transfer may occur *via* the tungstate framework of the heteropoly ion (a process responsible for "heteropoly blue" formation[18]). Thus a known outer-sphere electron transfer agent is being used as an oxidant for alkyl aromatics to determine whether such a process is feasible.

Experimental Section

The tungstocobaltates were prepared by literature methods.[7-9] The preparations are briefly described below.

Potassium hydrogen 12-tungstocobaltate(II) (1) was prepared by treating potassium 11-tungstodicobaltate(II)[7] with dilute hydrochloric acid. Partial evaporation of the resulting blue solution produced blue-green needles.

Potassium 12-tungstocobaltate(III) (2) was prepared by addition of solid potassium persulfate to a solution of the potassium 11-tungstodicobaltate(II) in 2 *M* H_2SO_4. The yellow solid was recrystallized three times from boiling water, resulting in yellow crystals.

Elemental and thermogravimetric analyses indicated that **1** was a 17-hydrate, $K_5H[Co^{II}O_4W_{12}O_{36}]\cdot 17\ H_2O$, and **2** was an 18-hydrate, $K_5[Co^{III}O_4W_{12}O_{36}]\cdot 18\ H_2O$.

Spectra.—Visible and ultraviolet spectra were determined on a Unicam SP800D spectrophotometer. The visible spectra of **1** and **2** were in agreement with those given by Simmons.[9]

The visible spectrum was used to analyze the extent of conversion of **2** to **1** in the oxidations described below. However, it was found that the intensity of the spectrum of **1** in water was significantly dependent on pH (although the position of the maximum at 16.06 kK was invariant); thus it was necessary to use a sodium acetate–acetic acid buffer (pH 4.6) for the analysis, which was performed as follows. The solid isolated from the heterogeneous oxidation (described below) was dissolved in a suitable amount of buffer solution and the visible spectrum recorded. The absorbances at 16.06 and 25.70 kK (A_1 and A_2, respectively) were read and the extent of conversion calculated from the known molar absorbances of **1** (218 and 130, respectively) and **2** (0 and 1225, respectively) by use of the equation

$$\%\ \text{conversion} = \frac{1225A_1}{218A_2 + 1095A_1} \times 100$$

(1) A preliminary account has appeared: A. W. Chester, *Chem. Commun.*, 352 (1969).

(2) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **91**, 6830 (1969).

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(4) A. W. Chester, E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *Inorg. Nucl. Chem. Lett.*, **5**, 277 (1969).

(5) R. D. Gillard, *J. Chem. Soc., A*, 917 (1967).

(6) D. L. Wood and J. P. Remeika, *J. Chem. Phys.*, **46**, 3595 (1967).

(7) L. C. W. Baker and T. P. McCutcheon, *J. Amer. Chem. Soc.*, **78**, 4503 (1956).

(8) L. C. W. Baker and V. E. Simmons, *ibid.*, **81**, 4744 (1959).

(9) V. E. Simmons, Ph.D. Dissertation, Boston University, 1963.

(10) L. C. W. Baker, V. S. Baker, K. Eriks, M. T. Pope, M. Shibata, O. W. Rollins, J. H. Fang, and L. L. Koh, *J. Amer. Chem. Soc.*, **88**, 2329 (1966).

(11) L. C. W. Baker in "Advances in the Chemistry of Coordination Compounds," S. Kirschner, Ed., The Macmillan Co., New York, N. Y., 1962, p 604.

(12) P. G. Rasmussen, *J. Chem. Educ.*, **44**, 277 (1967).

(13) K. Eriks, N. F. Yanonni, U. C. Agarwala, V. E. Simmons, and L. C. W. Baker, *Acta Crystallogr.*, **13**, 1139 (1960); N. F. Yanonni, Ph.D. Dissertation, Boston University, 1961.

(14) N. F. Yanonni, V. E. Simmons, K. Eriks, and L. C. W. Baker, Abstracts, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1959, p 26N.

(15) J. F. Keggin, *Proc. Roy. Soc., Ser. A*, **144**, 75 (1934).

(16) P. G. Rasmussen and C. H. Brubaker, Jr., *Inorg. Chem.*, **3**, 977 (1964).

(17) G. Geier and C. H. Brubaker, Jr., *ibid.*, **5**, 321 (1966).

(18) M. T. Pope and G. M. Varga, *ibid.*, **6**, 1249 (1966), and references cited therein.

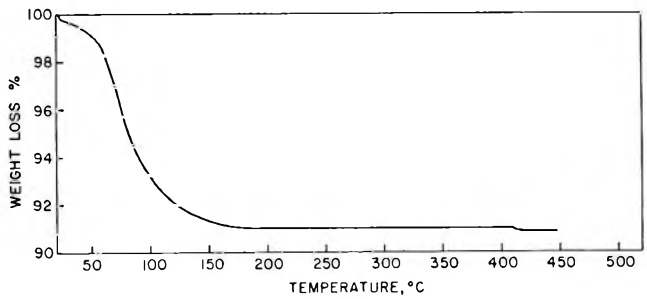


Figure 1.—Thermogravimetric analysis of $K_5[Co^{III}O_4W_{12}O_{36}]\cdot 18H_2O$ showing the loss of the last H_2O at ~420°.

Thermal Studies.—Thermogravimetric and differential thermal analyses (tga and dta) were performed on the Dupont 950 thermogravimetric analyzer and the Du Pont 900 differential thermal analyzer by Mr. A. Julian.

Gas Chromatography.—Gas chromatographic analyses were performed on an F & M research chromatograph (Model 810). The helium flow rate was 32 ml/min with a 10-ft silicone Se30 on Diataport column. A temperature program (6 min at 120°, heating to 250° at 10°/min, then isothermal at 250°) was used, with a sample volume of 5 μl.

Homogeneous Oxidation of Toluene by Potassium 12-Tungstocobaltate(III).—A solution of 20 g of 2 18-hydrate in a mixture of 15 ml of water and 75 ml of acetic acid was heated at reflux with 15 ml of toluene for 55 hr. After the mixture cooled, the solid was filtered and the filtrate evaporated. The resulting solid–liquid mixture was extracted with ether; the ether extract was dried over $MgSO_4$ and evaporated to give an oil. The oil was analyzed by gas chromatography and the major product was found to be benzyl acetate (confirmed by infrared spectrum). Small amounts of other components were found but not identified.

Heterogeneous Oxidation of Alkyl Aromatic Hydrocarbons by Potassium 12-Tungstocobaltate(III). Procedure.—Oxidations were performed in a glass-stoppered reaction vessels immersed in a constant-temperature bath at 96°. About 3 g (1 mmol) of **2** monohydrate (prepared by heating the 18-hydrate at 200°; see Results and Discussion) was covered with an excess (about 10 g) of hydrocarbon in the reaction vessel and placed in the bath for 100 hr.[19] The mixture was filtered into a tared filter flask and the solid analyzed for **1** and **2** as described above. The filtrate was partially evaporated *in vacuo* and analyzed by gas chromatography.

The products of the oxidation of toluene and *p*-xylene were established by comparison of ir and uv spectra and retention times with those of known samples. The identity of 2,4′,5-trimethyldiphenylmethane (from *p*-xylene) was established by the agreement of its ir and uv spectra with those given by Dannenberg, Neumann, and Dresler.[20] The products of the *o*- and *m*-xylene oxidations were assigned by analogy and by the similarity of the retention times to those of the toluene and *p*-xylene products.

Oxidations in the presence of benzene (cross-alkylation) were performed at 80.5°. Most of the benzene was removed in the partial evaporation of the product filtrate.

Results and Discussion

Dehydration of Potassium 12-Tungstocobaltate(III).—In preliminary experiments with 2 18-hydrate, large amounts of oxygenated products (alcohols and aldehydes) were formed, presumably from the lattice water. It was, therefore, desirable to use an anhydrous form for oxidations. However, tga indicated that only 17 mol of H_2O were lost upon heating to 200°, the remaining water being lost at about 420° (Figure 1). Dta studies showed an exotherm at approximately this temperature, indicating that loss of the last water leads to decomposition. The retention of 1 mol of water was confirmed in experiments at 200° in air.

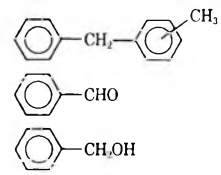
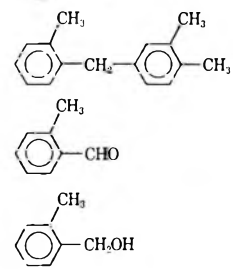
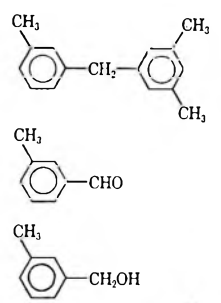
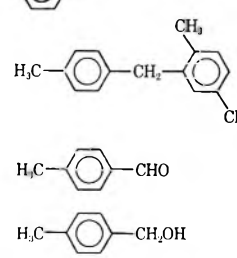
Oxidations were therefore carried out with the monohydrate. Use of the monohydrate led to increased yields of the diphenylmethane products (discussed below) and reduced quantities of the oxygenated materials.

The crystallographic data for potassium 12-tungstocobaltate(III)[13] do not show a unique water molecule in the structure. The water might reside between heteropoly frameworks, bonding them together. However, the occurrence of oxygenated products indicates that it is chemically reactive. The exact location and function of the unique water molecule is unknown at this time.

Oxidation Products.—The products, yields, and product distributions for the heterogeneous oxidation of toluene and the isomeric xylenes by $K_5[Co^{III}O_4W_{12}O_{36}]\cdot H_2O$ are given in Table I. The data for the

TABLE I

THE OXIDATION OF ALKYL AROMATIC HYDROCARBONS BY POTASSIUM 12-TUNGSTOCOBALTATE(III) MONOHYDRATE AT 96° (100 HR)

Substrate	Product[a]	Distribution wt, %	Yield, %[b,c]
Toluene		77 23 Trace	44
o-Xylene		61 33 6	26
m-Xylene		67 26 7	26
p-Xylene[d]		59 (40) 34 (43) 7 (17)	40 (12)

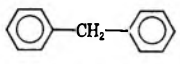
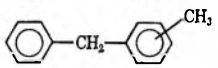
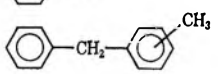
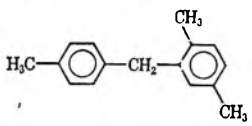
[a] Not all possible isomers are shown for the diphenylmethane derivatives. [b] Given only for diphenylmethane derivatives. [c] Based on Co^{III} consumed and a stoichiometry of $2Co^{III}$/hydrocarbon (see text). [d] Figures in parentheses represent the result of oxidation by the 18-hydrate.

(19) Air was not rigorously excluded.

(20) H. Dannenberg, H. G. Neumann, and D. D. von Dresler, *Justus Liebigs Ann. Chem.*, **674**, 152 (1964).

oxidation in an excess of benzene are given in Table II. Production of diphenylmethane in this case constitutes, in effect, an alkylation of benzene by the benzyl group.

TABLE II
OXIDATIONS IN THE PRESENCE OF EXCESS BENZENE AT 80.5°[a]

Substrate	Mol of C_6H_6/mol of substrate	Products[b]	Distribution, %	Yield, %
Toluene	12.0		66	Not determined
			32	
			2	
p-Xylene	15.3		45	66
			36	
			19	

[a] The monohydrate was used for these experiments; reaction time 100 hr. [b] Alcohols occurred only in trace amounts.

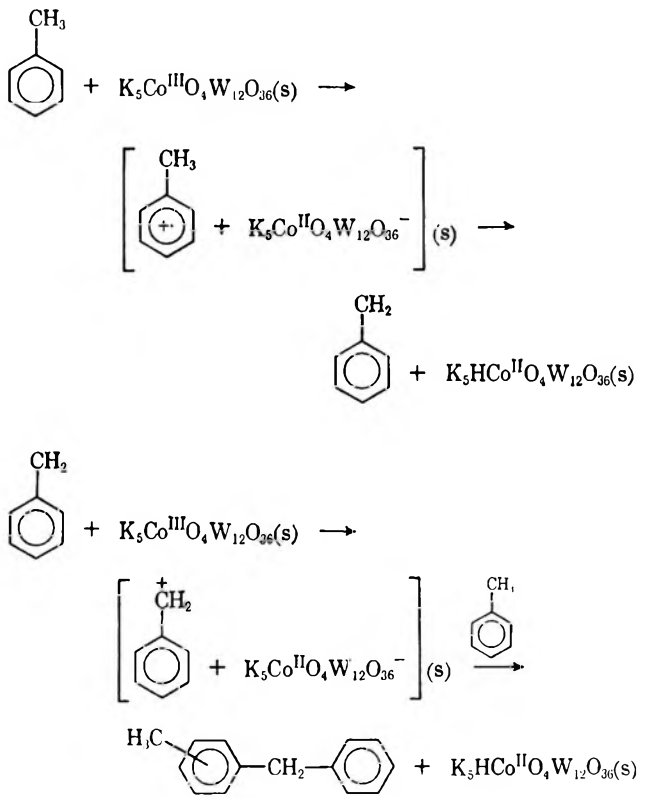
Mechanism.—It is well known that heteropoly ions oxidize many oxygen- and nitrogen-containing organic compounds with resultant formation of "heteropoly blues."[21] In all such oxidations, it is only the tungstate (or molybdate) framework that is reduced, not the central (hetero) atom. The present case thus constitutes the first example in which the central atom *alone* (tetrahedral Co^{III}) is the oxidizing agent and is reduced (to Co^{II}). The identity of the reduction product is clear from its visible spectrum, which is characteristic of tetrahedral Co^{II} and identical with that obtained with a known sample of **1**.

Studies of the behavior of the 12-tungstocobaltates in aqueous solution show that electron transfer is an outer-sphere process[16] and that the framework oxygens do not exchange with water.[17] The same is probably true in the oxidation of aromatic hydrocarbons: the oxidation occurs *via* outer-sphere electron transfer in which the heteropoly ion structure remains unchanged.

The diphenylmethane products could be formed by the attack of benzyl radicals or carbonium ions on the aromatic ring. However, benzyl radicals dimerize to form bibenzyl more rapidly than they add to aromatic rings. Since no bibenzyl products are observed, the benzyl radicals must be oxidized by the heteropoly ion to form benzyl carbonium ions. The benzyl radical can be formed by two possible paths: (a) hydrogen abstraction from a methyl group, followed by oxidation of the hydrogen atom to a proton, or (b) oxidation of the aromatic to a radical cation, followed by proton expulsion. Mechanism a seems less reasonable since there is no reason that the tungstate framework should accept a hydrogen *atom*. Also, this mechanism could not be operative in the oxidation of the radical to the carbonium ion, since no hydrogen abstraction would occur.

Mechanism b is more self-consistent. The electron transfer occurs *via* the overlap of the aromatic π system with tungstate framework "conduction" bands,[12,18] so that reduction of the framework occurs first. The framework, however, rapidly reduces the electronically less stable tetrahedral cobalt(III). The expulsion of the proton and its acceptance by the tungstate anion provides the charge balance necessary for a solid state reaction. The oxidation of the radical can occur by exactly the same process: electron transfer from the π system of the aromatic *via* the framework to the cobalt atom. The mechanism may be summarized for toluene as shown in Scheme I. The brackets indicate ion pairs formed within the solid. The steps leading to the ion pairs may in fact be equilibria. This sequence leads to a stoichiometry of $2Co^{III}$/hydrocarbon, and the yields of diphenylmethane derivatives in Tables I and II are calculated on this basis.

SCHEME I



The alcohol products result from the interaction of the carbonium ion with the remaining water in the 1-hydrate. The alcohol may be subsequently oxidized to the aldehyde in a manner similar to the above mechanism. A trace of unidentified high boiling compound is observed in the gas chromatographic analysis of the oxidation products, which may be an alcohol derived from the diphenylmethane derivative by oxidation as above.

The homogeneous oxidation of toluene in aqueous acetic acid (see Experimental Section) results in formation of benzyl acetate, indicating that a similar mech-

(21) A. W. Seiling, Jr., Ph.D. Dissertation, Indiana University, 1962; J. H. Bellman, D. B. Borders, J. A. Buehler, and A. W. Seiling, *Anal. Chem.*, **37**, 264 (1965).

anism is operative. The carbonium ion reacts with the acetic acid solvent to form the acetate.

The electron-transfer reactions may occur at or near the solid surface, or within the crystal lattice. The crystal is composed of channels surrounded symmetrically by six heteropoly ions.[13] The channels are probably large enough to allow some penetration by the aromatic hydrocarbon, and the immediate availability of other heteropoly ions accounts for the ease of carbonium ion formation. The carbonium ion would then either diffuse out to react with other hydrocarbon molecules or react with the water in the lattice to form alcohol.

The aromatic radical cation is formed by outer-sphere electron transfer. Inner-sphere electron transfer is eliminated by the stability and nondestruction of the tungstate framework, which totally screens the cobalt(III) oxidant from direct interaction with the aromatic π system.

It is also significant that the oxidation occurs by outer-sphere electron transfer in a heterogeneous system. Such reactions are usually thought to occur by direct coordination to a metal on a surface or in a crystal.

The above results indicate that it is unnecessary to seek an inner-sphere electron transfer mechanism in the oxidation of alkyl aromatics in homogeneous systems,[2-4] *e.g.*, by direct coordination, since outer-sphere electron transfer is feasible.

Registry No.—Potassium 12-tungstocobaltate(III), 12419-42-0; toluene, 108-88-3; *o*-xylene, 95-47-6; *m*-xylene, 108-38-3; *p*-xylene, 106-42-3.

Acknowledgments.—The author is indebted to Drs. E. I. Heiba, P. S. Landis, and E. J. Y. Scott for their advice and suggestions during this investigation, and for their helpful review of the manuscript.

Alkylation of N-Carbethoxy Tertiary Amines with Ethyl Bromoacetate

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The alkylation of ethyl 1-piperidineacetate (I), ethyl 4-morpholineacetate (II), ethyl N,N-diethylglycinate (III), and ethyl N,N-di-*n*-butylglycinate (IV) at 25, 40, 50, and 60° with ethyl bromoacetate in absolute methanol follows second-order kinetics. The k_2, ΔE, and ΔS values at 25° are 8.86, 0.89, 5.71, and 4.22 $\times 10^{-6}$ l./(mol sec), 17.2, 18.1, 14.6, and 14.8 kcal/mol, and 26.0, 27.6, 35.6, and 35.6 eu, respectively, for the above amines.

This research study investigated the effect of the structure of tertiary amines upon the reaction rate, the energy of activation, and the entropy of activation in the alkylation of the amines with ethyl bromoacetate in absolute methanol. The four amines investigated were ethyl 1-piperidineacetate (I), ethyl 4-morpholineacetate (II), ethyl N,N-diethylglycinate (III), and ethyl N,N-di-*n*-butylglycinate (IV).

The kinetics of the reactions were determined by potentiometric titration of the bromide ion produced using a silver nitrate solution with a glass electrode and a silver–silver bromide reference electrode. The reaction rates were determined from the slopes of the second-order plots. Activation energies were determined from the slope of the Arrhenius plots, and entropies of activation were calculated from the Eyring equation.

Results and Discussion

The experimental rate constant data are summarized in Table I where a is the initial molar concentration of ethyl bromoacetate and the tertiary amine in absolute methanol. The bimolecular rate constant, k_2, is defined by the familiar equation

$$dx/dt = k_2(a - x)^2 \quad (1)$$

The values of k_2 were calculated from the titration data by plotting

$$F(x) = x/(a - x) \quad (2)$$

vs. time where the slope of the plot is equal to ak_2. All of the $F(x)$ *vs.* t plots were linear to 200 hr and remained so for several samples for as long as 800 hr. The per cent of conversion to the quaternary salt varied from 2% for II at 20° to 83% for I at 60°. Most of the experiments were carried to 800 hr and longer, and deviations from linearity were noted in several runs at the higher temperatures. The average percentage error in determining $F(x)$ between two or more identical samples was 2.8% with a standard deviation of 6.1%. This percentage is based upon a population of 144 $F(x)$ determinations. Since the scatter of points increases with an increase of temperature, the accuracy of the $F(x)$ determinations was considerably improved for

TABLE I
Reaction Rate Constants[a]

Temp, °C (±0.1°)	$k_P \times 10^6$	$k_M \times 10^6$	$k_E \times 10^6$	$k_B \times 10^6$
5	1.47	0.106		
20	5.56	0.506		
25	8.86	0.890	5.71	4.22
40	33.9	4.00	20.8	15.2
50	80.5	10.0	49.4	32.6
60	150	23.1	86.7	60.0

Comparison of the Reaction Rates

Temp, °C, (±0.1°)	k_P/k_M	k_P/k_E	k_P/k_B	k_E/k_B
5	14.0			
20	11.0			
25	10.0	1.55	2.10	1.35
40	8.46	1.63	2.24	1.37
50	8.08	1.63	2.46	1.51
60	6.46	1.72	2.49	1.44

[a] P = ethyl 1-piperidineacetate, M = ethyl 4-morpholineacetate, E = ethyl N,N-diethylglycinate, B = ethyl N,N-di-*n*-butylglycinate.

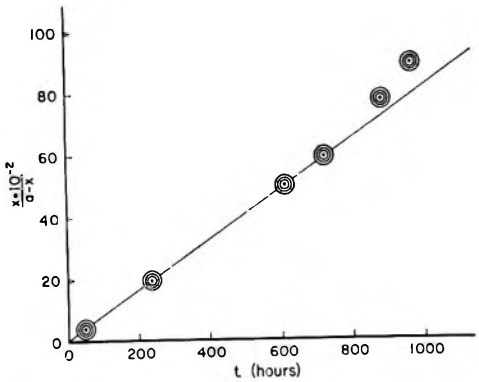

Figure 1.—Ethyl N,N-di-*n*-butylglycinate (25 ± 0.1°).

titrations below 200 hr. With a population of 76 F(x) determinations below 200 hr, the percentage error was 1.8% with a standard deviation of 2.3%. At least three samples were run at each temperature for each tertiary amine.

It has been reported that methanol will methanolyze an alkyl halide.[1] We experimentally determined the methanolysis reaction at 25 and 60° and found the following results for ethyl bromoacetate: room temperature for 240 hr, 0.55% methanolysis, and at 60° for 240 hr, 6.68% methanolysis. The alcoholysis reaction is evident in Figure 1 for the experimental points exceeding 800 hr.

The comparison between the rate constants is shown in Table I in ratio form. Compound I is much faster than II as expected with a hetero-oxygen atom in the ring. Compounds III and IV are much less reactive than the piperidine amine (I) because of the less basic character of the open-chain amines *vs.* the ring-structured amines (pK_a: piperidine, 11.22; morpholine, 8.36; diethylamine, 10.98; and di-*n*-butylamine, 11.25).[2] The longer alkyl chain of the *n*-butyl group does not appreciably decrease the rate of alkylation as compared to the ethyl group (k_E/k_B = 1.35 at 25°). These results are in agreement with Bunton who states that the steric factor of an aliphatic chain does not increase materially with increasing chain length beyond the ethyl group.[3]

The decrease in the ratio of k_P/k_M (Table I) as the temperature increases can be explained by the field-effect model in conjunction with the conformational isomers of morpholine (Figure 2). It is well established that a saturated six-carbon ring may exist in either the chair conformation or the boat conformation with a difference in energy of approximately 5 kcal/mol.[4] When a methylene group is replaced with a hetero atom, the energy of the boat form is less because of fewer interactions between consecutive methylene groups.[5] Consequently, one would expect II to have a higher concentration of the boat conformer as the temperature is increased.

In the boat conformation (Figure 2), the hetero-oxygen atom represents the negative end of a dipole which acts to increase the electron density on the nitrogen atom more so than in the chair conformation. Consequently, the reversed substituent effect of the oxygen atom should accelerate the rate of the alkylation and be more enhanced with a higher concentration of the boat conformers at the higher temperatures.[6]

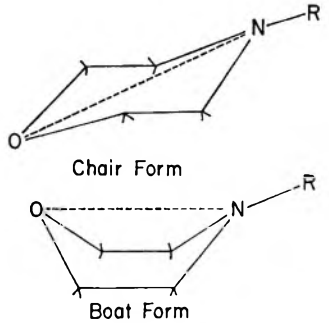

Figure 2.—Conformations of ethyl 4-morpholineacetate.

The experimental evidence for the reverse substituent effect was first reported by Stock[7] in his comparison of the pK_a values for dibenzobicyclo[2.2.2]octa-2,5-diene-9-carboxylic acid (pK_a = 6.04) and 16-chlorobicyclo[2.2.2]octa-2,5-diene-9-carboxylic acid (pK_a = 6.25). Roberts and Carboni[8] suggested a field effect for a chloro atom in *o*-chlorophenylpropiolic acid when the inductive effect was not so great as expected for the *o*-chloro group.

Since the entropy term (Table II) for II is more negative than for I, one can rule out a steric argument for a rate increase. If II had a preferred conformation for a more favorable attack by the ethyl bromoacetate, then one would expect to find the entropy term less negative. The entropy term for II is probably more negative than for I because of the steric interference that may result for the hetero-oxygen atom and the carboxyl oxygen atoms of the two N-carbethoxymethyl groups.

TABLE II
RATE CONSTANTS, ACTIVATION ENERGIES, AND ENTROPIES FOR TERTIARY AMINES AT 25°

Amine	$k \times 10^6$, l./(mol sec)	ΔE, kcal/mol	$-\Delta S$, cal/(mol deg)
N-Carbethoxymethylpiperidine (I)	8.86	17.2	26.0
N-Carbethoxymethylmorpholine (II)	0.89	18.1	27.6
Ethyl N,N-diethylglycinate (III)	5.71	14.6	35.6
Ethyl N,N-di-*n*-butylglycinate (IV)	4.22	14.8	35.6

The activation energies (Table II) indicate no irregularities from what one would predict. The close agreement between III and IV is justified if one accepts the steric similarity[3] between the *n*-butyl and the ethyl groups.

The larger (less negative) entropy terms for III and IV compared to I and II are undoubtedly the results of restricting the freedom of movement of the alkyl groups in the quaternary ammonium salt product compared to the tertiary amine reactant. In the case of morpholine and piperidine, there is no restriction of movement in

(1) B. D. Coleman and R. M. Fuoss, *J. Amer. Chem. Soc.*, **77**, 5472 (1955).
(2) H. K. Hall, Jr., *ibid.*, **79**, 5443 (1957).
(3) C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Co., New York, N. Y., 1963, p 27.
(4) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962).
(5) W. D. Kimler and A. C. Huntric, *J. Amer. Chem. Soc.*, **78**, 3369 (1956).
(6) *Note:* Solvation, as suggested by a reviewer, may play an important part in explaining these small differences in energy since piperidine could be solvated quite differently from morpholine.
(7) R. Golden and L. M. Stock, *ibid.*, **88**, 5928 (1966).
(8) J. D. Roberts and R. A. Carboni, *ibid.*, **77**, 5554 (1955).

the alkyl groups in going from the tertiary amine to the salt because they are part of the heterocyclic ring.

The activation energies and frequency factors of the study compared favorably with those for triethylamine and ethyl iodide as reported by Wolff[9] (Table III).

TABLE III
FORMATION OF QUATERNARY AMMONIUM SALTS (100°)
(ETHYL IODIDE AND TRIETHYLAMINE)

Solvent	$k \times 10^6$, l./(mol sec)	E, kcal/mol
Acetone	26.5	11.9
Nitrobenzene	138.3	11.6

Experimental Section

Compounds I (bp 50° at 0.150 mm), II (bp 68° at 0.60 mm), III (bp 50° at 3.54 mm), and IV (bp 75° at 1.15 mm) were prepared by reacting ethyl bromoacetate with a one molar excess of the respective secondary amine. All four tertiary amines were purified by distillation through an annular spinning-band[10] column under reduced pressure. The purity of the tertiary amine was established by vpc.[11]

To establish the identity of the tertiary amines, each amine (compound IV was an exception) was converted to a quaternary ammonium salt by reaction of the tertiary amine with ethyl bromoacetate. Compound I formed N,N-dicarbethoxymethylpiperidinium bromide. The diester was recrystallized from absolute ethanol, mp 134–134.5°.

Anal. Calcd for $C_{13}H_{24}O_4NBr$: C, 46.16; H, 7.15; N, 4.14; mol wt, 338.2. Found: C, 46.22; H, 7.03; N, 4.12; mol wt ($AgNO_3$ titration), 339.6.

Compound II formed N,N-dicarbethoxymethylmorpholium bromide. The diester was recrystallized from absolute ethanol, mp 157–158°.

Anal. Calcd for $C_{12}H_{22}O_5NBr$: C, 42.36; H, 6.52; N, 4.12; mol wt, 340.2. Found: C, 42.42; H, 6.32; N, 3.97; mol wt ($AgNO_3$ titration), 344.2.

Compounds III and IV failed to form a solid ester when treated with ethyl bromoacetate in absolute methanol. Consequently, the viscous diesters were hydrolyzed with 48% HBr refluxing for 2 hr. The diethyl N,N-dicarboxymethylammonium bromide was recrystallized from glacial acetic acid, mp 172–174°.

Anal. Calcd for $C_8H_{16}O_4NBr$: C, 35.57; H, 5.97; N, 5.19; mol wt, 270.13. Found: C, 35.56; H, 5.92; N, 5.19; mol wt ($AgNO_3$ titration), 270.2.

Compound IV could not be converted successfully to the quaternary ammonium diester or diacid. Consequently, the identity of the amine was established by comparing its boiling point, infrared spectrum, and vpc retention time with those of III. These comparisons indicated that compound IV had been successfully prepared.

Sample Preparation.—The samples for the kinetic study were prepared by weighing in separate flasks to ±0.1 mg sufficient tertiary amine and ethyl bromoacetate to make 50 ml of 0.0500 *M* solution. Each of these flasks was diluted with approximately 20 ml of absolute methanol (Baker Analyzed Reagent) and placed in a constant-temperature bath capable of maintaining a temperature of ±0.1°. Each sample of tertiary amine and ethyl bromoacetate was mixed in preheated 50-ml volumetric flasks and diluted with preheated methanol to 50 ml which established each sample at 0.0500 *M* in tertiary amine and ethyl bromoacetate. Three duplicate samples of each compound were prepared and studied at the same time. No correction was made for the expansion of the glassware or the solvent.

Procedure for Potentiometric Titration.—Three samples of a given compound at each temperature were titrated at 15-min intervals. From each of these samples, three 1.00-ml aliquots were diluted with 10.0 ml of cold 0.10 *N* H_2SO_4 within 30 sec of each other. Aliquots were titrated within 10 min after being withdrawn.

The bromide ion was titrated with 0.0500 *M* $AgNO_3$ from a 10-ml graduated buret. The Beckman expandomatic pH meter with a Beckman No. 39167 glass electrode and a laboratory constructed Ag|AgBr electrode were used in the titration. The accuracy of this technique was established by titrating 1.00-ml aliquots of 0.0050 *M* tetra-*n*-butylammonium bromide in 10 ml of 0.10 *N* H_2SO_4. The addition of 1.00 ml of ethyl bromoacetate did not interfere with the determination of a standard bromide ion concentration.

Silver nitrate was added in 0.05-ml increments until the end point was passed as indicated by a 100 mV or more change on the expanded scale.

Registry No.—Ethyl bromoacetate, 105-36-2; I, 23853-10-3; II, 3235-82-3; III, 2644-21-5; IV, 2644-24-8; N,N-dicarbethoxymethylpiperidinium bromide, 6262-05-6; N,N-dicarbethoxymethylmorpholium bromide, 23853-15-8; diethyl N,N-dicarboxymethylammonium bromide, 23853-16-9.

(9) H. G. Grimm, H. Reif, and J. Wolff, *Z. Phys. Chem.*, **B13**, 301 (1931).
(10) Nester–Faust annular spinning-band distillation column, Model NFT-50.
(11) Beckman GC-2A with thermotrac temperature programmer, 6-ft, 0.25-in. silicone column.

The Acid-Catalyzed Nitramine Rearrangement. VI. Diversion of the Rearrangement[1-3]

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The aromatic nitramine rearrangement produced lowered yields of nitroanilines and more aromatic amine and nitrous acid in the presence of a variety of reducing agents (iodide and thiocyanate ions, sulfur dioxide, thiourea, aromatic amines, and phenols). The rate was not affected by the presence of the reductant, indicating that diversion of the reaction occurs after the rate-determining step. The effect of the concentration of the diverting agent was unusual and can be interpreted by a mechanism in which the protonated nitramine undergoes N-N bond cleavage to produce a pair of caged radicals which can rebond to form precursors of the nitrated products or can undergo reversible dissociation to free radicals capable of being reduced.

It was recognized very early in the study of the aromatic nitramine rearrangement that, under certain conditions, a portion of the nitramine could be diverted from the isomerization pathway. For example, although N-nitro-2,4-dichloroaniline was converted principally into 2-nitro-4,6-dichloroaniline by nitric, sulfuric, hydrochloric, or perchloric acid,[4] a quantitative yield of 2,4-dichlorobenzenediazonium bromide was formed in the presence of hydrobromic acid.[5] The product of reaction of N-2,4-trinitro-N-methylaniline with concentrated sulfuric acid was 2,4,6-trimtro-N-methylaniline unless *p*-xylene was added to the reaction mixture. In the latter instance, 2,4-dinitro-N-methylaniline resulted.[6] Seldom does the rearrangement of a nitramine produce a quantitative yield of nitroaniline. The systematic study of the effect of apparently extraneous substances on the course of nitramine rearrangement reported in this paper leads to important conclusions about the course of the reaction.

Results and Discussion

Nature of Diverting Agents.—A cursory survey of the influence of various compounds on the course of the rearrangement of N-nitro-N-methylaniline was made. This was accomplished by comparison of the absorbances of the product mixtures from reactions to which various concentrations of different reagents had been added. The absorbance at 410 mμ was utilized for the comparison, since the maximum absorption of the combined nitroaniline products (and also of *p*-nitro-N-methylaniline) occurs at this point. The results are summarized in Table I.

The data in Table I indicate that the lowered yields of nitroanilines cannot be associated with the nucleophilicity of the added substance. Thus, bromide ion, which is a good nucleophile, was much less effective in diverting rearrangement than was *p*-cresol, which is a poor nucleophile. The ability of a reagent to scavenge nitrous acid also seems insignificant as a determinant. Thus the effect of sulfamic acid, which reacts selectively and readily with nitrous acid, was much different from that of iodide ion or phenol. The single common feature of the reagents that were effective in diverting the nitramine rearrangement is that they are easily oxidized, *i.e.*, they are reducing agents.

TABLE I

EFFECTS OF ADDED SUBSTANCES ON THE YIELDS OF REARRANGEMENT PRODUCTS FROM N-NITRO-N-METHYLANILINE[a]

Substance	M	A[b]	Substance	M	A[b]
None	...	0.642	Sulfamic acid	0.5	0.644
$LiClO_4$	2.0	0.665	Thiourea	0.05	0.436
$LiNO_3$	1.0	0.660	*N*-Methylaniline	0.01	0.533
LiCl	1.0	0.659	*p*-Toluidine	0.01	0.526
LiBr	1.0	0.622	Phenol	0.01	0.558
NaSCN	1.0	0.475	*p*-Cresol	0.005	0.507
NaI	0.01	0.417	2,4-Xylenol	0.005	0.488
$NaHSO_3$	0.05	0.468	Resorcinol	0.05	0.475
SO_2	0.5	0.475	1-Naphthol	0.001	0.443
H_3PO_2	0.03	0.616	Hydroquinone	0.001	0.430

[a] $HClO_4$ = 0.503 *M*, T = 40.0°. [b] Absorbance of reaction mixture after treatment with ammonium sulfamate and dilution with acetate buffer.

Products of the Diverted Reaction.—Quantitative determination of the products formed in the presence of diverting agents proves that reduction occurs. The proportions of N-methylaniline and nitrite ion were increased, while the amounts of *o*- and *p*-nitro-N-methylaniline decreased (Table II). Nitrite ion and N-methylaniline involve a lower oxidation state for the nitrogen atoms than do N-nitro-N-methylaniline or *o*- or *p*-nitro-N-methylaniline.

TABLE II

PRODUCTS OF REARRANGEMENT OF N-NITRO-N-METHYLANILINE[a] IN THE PRESENCE OF DIVERTING AGENTS (PER CENT YIELD)

	Diverting agent			
Product	None	*p*-HO-C_6H_4OH[b]	α-$C_{10}H_7OH$[c]	NaI[d]
o-Nitro-N-methylaniline	49	38	39	...
p-Nitro-N-methylaniline	32	18	18	...
N-Methylaniline	10	41	40	43
Nitrite ion	13	41	...	...

[a] $HClO_4$ = 0.503 *M*, *T* = 40.0°. [b] 0.001 *M* hydroquinone. [c] 0.001 *M* α-naphthol. [d] 0.01 *M* NaI.

Influence of Diverting Agents on Rates.—The formation of aromatic amine and nitrous acid could occur

(1) Previous papers in this series: (a) W. N. White, D. Lazdins, and H. S. White, *J. Amer. Chem. Soc.*, **86**, 1517 (1964); (b) W. N. White, C. Hathaway, and D. Huston, *J. Org. Chem.*, **35**, 737 (1970); (c) W. N. White and J. R. Klink, *ibid.*, **35**, 965 (1970); (d) W. N. White, J. T. Golden, and D. Lazdins, *ibid.*, **35**, 2048 (1970).

(2) Part of this work has been reported in a preliminary form: W. N. White, J. R. Klink, D. Lazdins, C. Hathaway, J. T. Golden, and H. S. White, *J. Amer. Chem. Soc.*, **83**, 2024 (1961).

(3) This work was supported by Grants G-7345 and GP-1970 from the National Science Foundation.

(4) K. J. P. Orton, *Chem. News*, **106**, 236 (1912).

(5) K. J. P. Orton, *Brit. Assoc. Advan. Sci. Rep.*, 115 (1908).

(6) E. D. Hughes and G. T. Jones, *J. Chem. Soc.*, 2678 (1950).

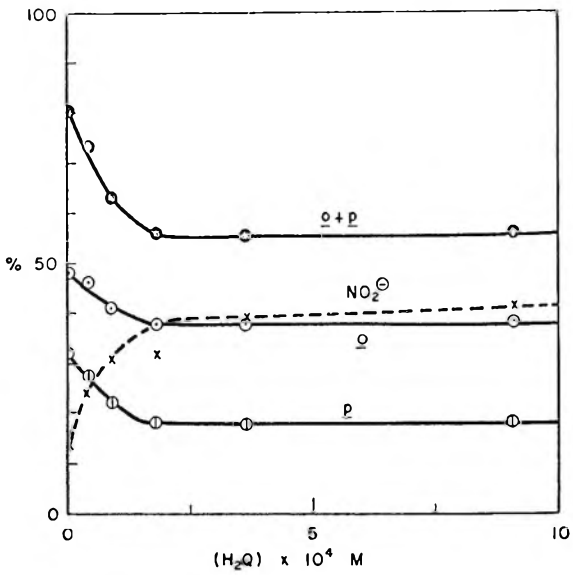

Figure 1.—Percentages of *o*- and *p*-nitro-N-methylaniline and nitrite ion formed in the rearrangement of N-nitro-N-methylaniline in the presence of varying amounts of hydroquinone (H_2Q) (40°, 0.503 *M* $HClO_4$): ⊙, per cent of *o*-nitro-N-methylaniline; ⊕, per cent of *p*-nitro-N-methylaniline; ●, sum of percentages of *o*- and *p*-nitro-N-methylaniline; and ×, per cent of nitrite ion.

through direct reduction of the nitramine by the diverting agent. In such a case there would be two kinetic pathways for disappearance of the nitramine (rearrangement and reduction) compared with one (rearrangement) under normal conditions, and thus the reaction should be faster in the presence of diverting reagents. However, it was found that the rate of reaction of N-nitro-N-methylaniline was unaffected by added reducing agents (Table III). This indicates that the incursion of the diverting agent occurs after the rate-determining step, which normally leads to rearrangement. Thus there is a common route and common intermediates for rearrangement and diversion.

TABLE III
RATE OF REARRANGEMENT OF N-NITRO-N-METHYLANILINE[a] IN THE PRESENCE OF DIVERTING AGENTS

Diverting agent	*M*	10^3k, sec^{-1}
None	...	1.06 ± 0.06
Hydroquinone	0.001	1.00 ± 0.02

[a] $HClO_4$ = 0.503 *M*, *T* = 40.0°.

Effect of the Concentration of Diverting Agent.—The influence of the concentration of the reducing agent on the product composition was very helpful in defining the mechanism of the nitramine rearrangement. As the concentration of hydroquinone was increased from 0 to *ca.* 0.00015 *M*, the percentages of *o*- and *p*-nitro-N-methylaniline formed from N-nitro-N-methylaniline decreased. Thus a bimolecular process involving the diverting agent and the nitramine or an intermediate derived from it was occurring. However, increasing the hydroquinone concentration above 0.00015 *M* caused no further effect on yield. The amount of nitrite ion produced behaved in about the same way except that it first increased before becoming constant at higher reducing agent concentrations. These results are presented graphically in Figure 1.

These findings indicate that the diverting agent is not reacting with the free or protonated nitramine, nor with the intermediate resulting directly from the rate-determining step. Any of these processes would involve direct competition between the pseudo-first-order rearrangement and second-order diversion, so that increasing the concentration of reducing agent should eventually decrease the yields of nitroanilines to zero. The species being reduced must not be on the rearrangement pathway, but must be in equilibrium with an intermediate that is. Furthermore, the kinetic effect of diverting agent (*vide supra*) shows that this latter intermediate is one that is formed after the rate-limiting step.

The situation is reminiscent of that found for the scavenging of α-isobutyronitrile radicals formed in the decomposition of azobisisobutyronitrile,[7] and an analogous interpretation appears appropriate. Substituent-effect studies[1c] suggested that the protonated nitramine undergoes N–N bond cleavage to form an anilinium radical and nitrogen dioxide. These species are undoubtedly held in a solvent cage for a short period of time, during which they may combine to form nitroanilines. Alternatively, dissociation to free radicals may occur. These radicals may reassociate to the caged pair and lead to nitrated products or they may react with a hydrogen donor to yield nitrous acid and amine. Caged species are ordinarily inert to scavengers. As the concentration of reducing agent is increased, more of the dissociated radicals are reduced and fewer return to the solvent cage and produce nitroanilines. Finally, a point is reached at which all of the free radicals formed are being reduced and a further increase in the amount of diversion is not possible. If the rate of rebonding of the caged radicals is similar to the rate of dissociation, then rearrangement and diversion will occur simultaneously and it will be impossible to completely eliminate rearrangement by increasing the reducing agent concentration. The mechanism implied by these findings and considerations is indicated in Chart I.

The nitrated product from rearrangement of N-nitro-N-methylaniline in the presence of 0.00015 *M* or more hydroquinone arises from caged radicals formed directly and entirely from protonated nitramine (Chart I, step 2 followed only by steps 3*o* and 3*p*). The proportion of *o*- and *p*-nitroanilines produced under these conditions is different from that obtained under normal circumstances in the absence of reductant (step 2 followed by steps 3*o*, 3*p*, 4f, and 4r). This implies that the isomer ratio resulting from free-radical reassociation (step 4r followed by steps 3*o* and 3*p*) is different from that derived from the directly formed caged radicals (step 2 followed by steps 3*o* and 3*p*). It is possible to estimate the proportions of isomers formed in each sequence. The results are listed in Table IV and suggest that the "structure" or average configuration of the caged radical pair differs depending on its source (step 2 or step 4r).

(7) G. S. Hammond, J. N. Sen, and C. E. Boozer, *J. Amer. Chem. Soc.*, **77**, 3244 (1955).

CHART I

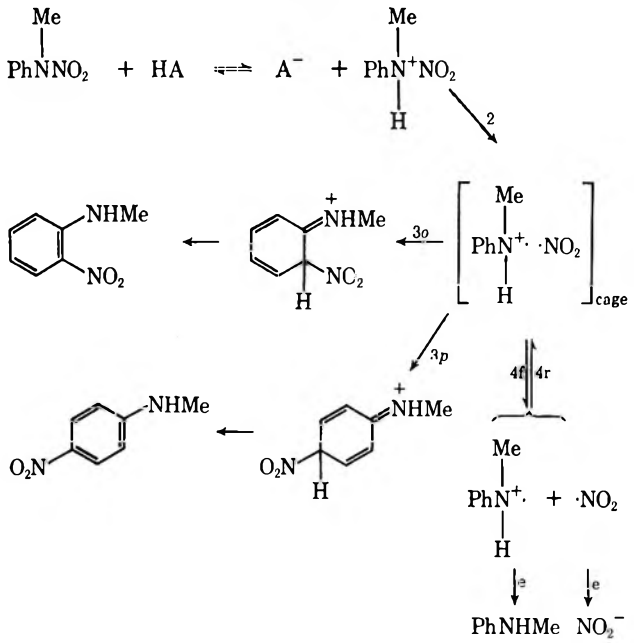

TABLE IV

COMPOSITION OF REARRANGEMENT PRODUCT FROM DIFFERENT MECHANISTIC SEQUENCES (PER CENT YIELD)

Product	Sequence of steps[a] 2 + 3o, 3p	4r + 3o, 3p
o-Nitro-N-methylaniline	68	31
p-Nitro-N-methylaniline	32	69

[a] See Chart I.

Since radical reassociation (step 4r) is an equilibrium process, the resulting caged pair probably possesses the lowest energy, most stable average configuration. The product composition in this case is therefore due to the operation of ordinary electronic and steric effects. The much larger amount of *crtho* isomer in the product formed directly from the nitramine (step 2 followed by steps 3*o* and 3*p*) might result if recombination of the radicals is very rapid and occurs before the nitro group has had an opportunity to migrate far from its origin.

The results of this study of the diversion of the aromatic nitramine rearrangement by reducing agents add considerable detail to the mechanism of the isomerization process and support the previously proposed radical mechanism[1c] (Chart I)

Experimental Section

N-Nitro-N-methylaniline.—This compound was prepared by alkaline nitration of aniline followed by methylation of the resulting N-nitroaniline without isolation of the latter substance.[8]

Rearrangement Conditions.—A 2.00-ml aliquot of a solution of N-nitro-N-methylaniline in dioxane was added to a previously thermostatted (40.0 ± 0.5°) solution of 5.00 ml of 5.03 *M* perchloric acid, diverting agent (if present), and *ca.* 40 ml of water in a 50-ml volumetric flask. The contents of the flask were made up to volume with water at 40° and the mixture was shaken and thermostatted at 40.0 ± 0.5° for 60 min. Aliquots of this solution were then analyzed for absorbance at 410 mμ, the percentage of *o*- and *p*-nitro-N-methylaniline present, the nitrous acid content, and/or the amount of N-methylaniline using the following procedures.

Total Absorbance.—A 5.00-ml aliquot of the rearrangement solution was heated with 5.00 ml of 5% ammonium sulfamate solution in a 25-ml volumetric flask at 80° for 30 min. The solution was cooled and acetate buffer (15.0 g of sodium acetate trihydrate, 50.0 ml of water, and 50.0 ml of acetic acid) was added to bring the volume to 25.0 ml. The mixture was shaken and its absorbance at 410 mμ was determined.

Determination of *o*- and *p*-Nitromethylaniline.—Spectrophotometric determination of these components of the reaction mixture was accomplished by the procedure described previously.[1a]

Determination of Nitrous Acid.—Nitrous acid was assayed by a colorimetric method.[1a]

Determination of N-Methylaniline.—^{14}C-labeled nitramine was rearranged as described above. The percentage of N-methylaniline formed was determined by isotope dilution analysis.[1a]

Rates of Rearrangement.—The methods described in previous papers[1b,c] in this series were utilized to determine the kinetic constants for the acid-catalyzed rearrangement of N-nitro-N-methylaniline in the presence and absence of diverting agents.

Registry No.—N-Nitro-N-methylaniline, 7119-93-9.

(8) W. N. White, E. F. Wolfarth, J. R. Klink, J. Kindig, C. Hathaway, and D. Lazdins, *J. Org. Chem.*, **26**, 4124 (1961).

A New Synthesis of Isoxazoles from 1,4 Dianions of Oximes Having an α Hydrogen. Mass Spectrometry[1]

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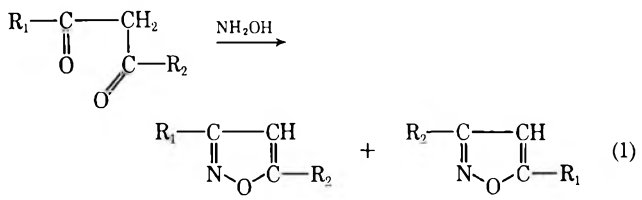
The 1,4 dianions of deoxybenzoin oxime, acetophenone oxime, and *para*-substituted acetophenone oximes were prepared and condensed with aromatic esters followed by acid cyclization to give unsymmetrical 3,4,5-tri- and 3,5-disubstituted isoxazoles. The synthesis of other isoxazole types, using various oxime 1,4 dianions, by this convenient and unequivocal method is presented. Mass spectra of unsymmetrical isoxazoles are also discussed.

Probably the most general method for the synthesis of isoxazoles involves the condensation–cyclization of hydroxylamine with a β diketone; the reaction of unsymmetrical β diketones or their enol ethers with hydroxylamine gives unsymmetrically substituted isoxazoles; however, the reaction can and does give both possible isomers, although some selectivity has been achieved by controlling the pH of the reaction[3-6] (eq 1).

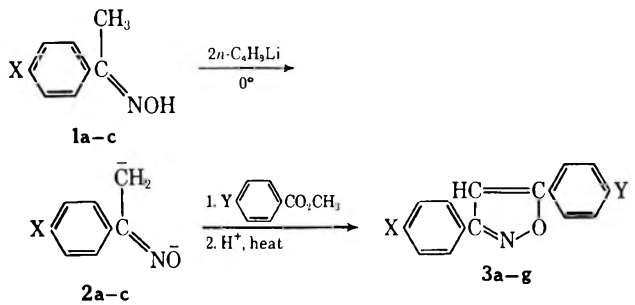


(1)

The present paper describes an unequivocal method for the synthesis of substituted isoxazoles from the oxime of a ketone having an α hydrogen and from an aromatic ester. The oxime was converted to its 1,4-dilithio salt with 2 molar equiv of *n*-butyllithium[7] and 0.5 molar equiv of ester was added.[8] The presumed intermediate keto oximes were not isolated, but were cyclized directly under acidic conditions to give substituted isoxazoles in good yields.

An unequivocal synthesis of unsymmetrical 3,5-diarylisoxazoles was undertaken by aroylation of several acetophenone and *para*-substituted acetophenone oxime dianions with methyl benzoate or methyl *para*-substituted benzoates followed by acid cyclization to the isoxazole (Scheme I). Dianion **2** was conveniently formed at 0° instead of −80°[7] by the reaction of 2 mol of *n*-butyllithium/mol of oxime. Aroylation was accomplished in the manner of the Claisen aroylation[8] with 0.5 mol of ester/mol of **2**, and upon acid cyclization isoxazoles **3a–g** were obtained in 50–60% yield

SCHEME I



based upon the ester. The structures of isoxazoles **3a–g** were supported by analysis and/or absorption spectra. The melting points of known compounds **3a–e** were in agreement with those previously reported.[9]

The infrared spectrum of **3a** was essentially identical with the spectrum reported for this compound.[10] The infrared spectrum of each of the other six isoxazoles **3b–g** was consistent with the assigned structure. For the three pairs of isomeric 3,5-diarylisoxazoles **3b** and **3d**, **3c** and **3e**, and **3f** and **3g**, the infrared spectrum of one isomer was similar to but not identical with that of the other isomer. No consistent pattern was discernible in the three pairs of spectra to permit identification of one isomer of such a pair of unsymmetrically disubstituted isoxazoles.

The nmr of the seven isoxazoles **3a–g** contained aromatic absorptions, plus a singlet due to the methoxy group in **3c,e–g**. Each isoxazole had an absorption signal in the region δ 6.8–7.2[11] which was assigned to the proton at the 4 position of the isoxazole ring. When this resonance signal was not complicated by other aromatic absorptions, it appeared as a singlet which integrated for one proton.

In a manner similar to the procedure described above, certain 5-*para*-substituted 3,4,5-triarylisoxazoles were prepared. The dianion of deoxybenzoin oxime **4** was prepared and condensed with various methyl and methyl *para*-substituted benzoates to give the corresponding isoxazoles **5a–c** in 75–85% yield (Scheme II). The structures of **5a–c** were confirmed by absorption spectra and compounds **5b** and **5c** were also supported by analysis (Table I).

The general applicability of this method of isoxazole synthesis was partially investigated. Isoxazoles were successfully prepared by the condensation–cyclization

(1) Supported by the Public Health Service, Research Grant CA-04455 from the National Cancer Institute and the National Science Foundation.

(2) (a) National Aeronautics and Space Administration Trainee, 1967–1969. (b) Deceased.

(3) See A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17, R. L. Wiley, Ed., John Wiley & Sons, Inc., New York, N. Y., 1962, Chapter 1.

(4) See, for example, the discussion in K. M. Johnston and R. G. Schotter, *J. Chem. Soc., C*, 1774 (1968).

(5) (a) See R. A. Barnes, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 454; (b) N. K. Kochetkov and S. D. Sokolov, *Advan. Heterocycl. Chem.* **2**, 366 (1963).

(6) See U. Teurck and H. Behrenger, *Chem. Ber.*, **98**, 3020 (1965).

(7) F. E. Henoch, K. G. Hampton, and C. R. Hauser, *J. Amer. Chem. Soc.*, **91**, 676 (1969).

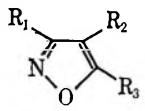
(8) The proportions correspond to the use of 2 molar equiv of base and ketone and one of ester in the analogous acylation of a ketone, which has been one of the two recommended procedures for such Claisen condensations with ester; see also C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 113 (1954).

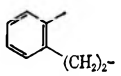
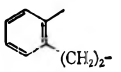
(9) C. Weygand, E. Bauer, and W. Heynemann, *Justus Leibigs Ann. Chem.*, **459**, 123 (1927).

(10) A. R. Katritsky and A. J. Boulton, *Spectrochim. Acta*, **17**, 238 (1961).

(11) K. Sirakawa, O. Aki, S. Tsushima, and K. Konishi, *Chem. Pharm. Bull.* (Tokyo), **14**, 89 (1966).

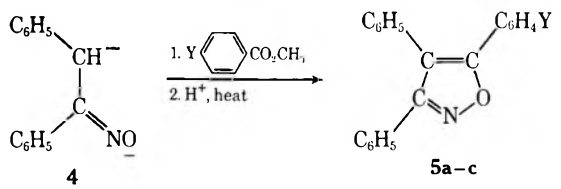
TABLE I



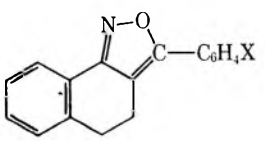
Compd	R_1	R_2	R_3	% yield	Mp, °C	Lit. mp, °C (ref)	Mol wt M+ [a]	Nmr, δ [b] C_4 H isoxazole
3a	C_6H_5–	H	C_6H_5–	59	141–142.5 [c]	141 [f]		6.83
3b	C_6H_5–	H	*p*-C_6H_4Cl–	59	179.5–180.5 [d]	178–179 [g]	255	7.18
3c	C_6H_5–	H	*p*-$C_6H_4OCH_3$–	51	127–128 [c]	128 [i]	251	6.89
3d	*p*-C_6H_4Cl–	H	C_6H_5–	65	176.5–177.5 [d]	175 [h]	255	7.19
3e	*p*-$C_6H_4OCH_3$–	H	C_6H_5–	54	120.5–121.5 [c]	121 [i]	251	6.75
3f	*p*-C_6H_4Cl–	H	*p*-$C_6H_4OCH_3$–	66	179–181 [d,e]		285	7.22
3g	*p*-$C_6H_4OCH_3$–	H	*p*-C_6H_4–Cl–	54	185.5–186.5 [d,e]		285	7.04
5a	C_6H_5–	C_6H_5–	C_6H_5–	72	210–211 [c]	210 [j]	297	
5b	C_6H_5–	C_6H_5–	*p*-C_6H_4Cl–	80	174–176 [c,e]		331.0764 (C) 331.0760 (F)	
5c	C_6H_5–	C_6H_5–	*p*-$C_6H_4OCH_3$–	79	162–163 [c,e]		327.1259 (C) 327.1257 (F)	
6a			C_6H_5–	19	87–89 [c,e]			
6b			*p*-$C_6H_4OCH_3$	37	146–147 [c,e]		277.1103 (C) 277.1102 (F)	
7a	$-(CH_2)_3-$		C_6H_5–	74	106–107 [c,e]	108–109 [k]	185	
7b	$-(CH_2)_4-$		C_6H_5–	62	65–67 [c]	67 [k]	199	
8a	*p*-$C_6H_4OCH_3$–			47	139–141 [c,e]		252.0899 (C) 252.0899 (F)	6.85
8b	C_6H_5–	H	$-CH_2C_6H_5$	28	79–80 [c]	81 [l]	235.0997 (C) 235.0992 (F)	6.82

[a] Molecular weight determined by low- and high-resolution mass spectrometry. C = calculated; F = found. [b] Trifluoroacetic acid solvent. [c] Recrystallized from ethanol. [d] Recrystallized from benzene. [e] Satisfactory analyses (±0.30%) for C, H, N, and Cl (where applicable) were obtained for all new compounds reported (Editor). [f] C. Goldschmidt, *Chem. Ber.*, **28**, 2540 (1895). [g] P. Grunanger, *Gazz. Chim. Ital.*, **89**, 1771 (1959). [h] G. Bianchetti, D. Pocar, and P. D. Croce, *ibid.*, **93**, 1714 (1963). [i] Reference 9. [j] D. E. Worrall, *J. Amer. Chem. Soc.*, **57**, 2299 (1935). [k] G. Bianchetti and P. Grunanger, *Chim. Ind.* (Milan), **46**, 425 (1964). [l] G. S. d'Alcontres and G. L. Vecchio, *Gazz. Chim. Ital.*, **90**, 1239 (1960).

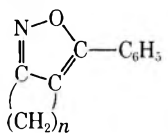
SCHEME II



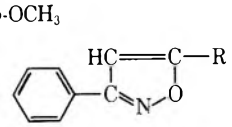
of methyl or a methyl *para*-substituted benzoate with the oxime dianions of α-tetralone, cyclopentanone, and cyclohexanone. The yields of the isoxazoles obtained ranged from 19 to 74% (**6a**,**b** and **7a**,**b**). Isoxazoles **6a**



6a, X = H
b, X = *p*-OCH_3



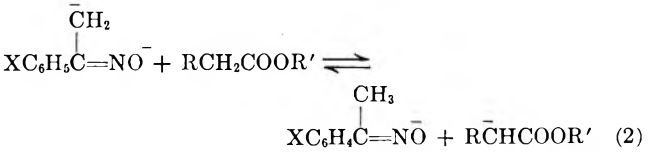
7a, *n* = 3
b, *n* = 4



8a, R =

b, R = $-CH_2C_6H_5$

and **b** were characterized by analysis and absorption spectra. The yields reported (19 and 37%) are probably not the maximum obtainable, because of diminished solubility of this dianion compared with the solubility of the dianions previously mentioned. Isoxazoles **7a** and **7b** are known and confirmation of structure was possible from comparison of melting points with those reported and their absorption spectra. The ester component was also varied, and isoxazoles were prepared by condensation–cyclization with ethyl nicotinate and ethyl phenylacetate to give **8a** and **8b** in yields of 47 and 28%, respectively. Interestingly, precursor pyridyl β diketones for **8a** have not been reported; thus the present procedure represents a convenient and direct synthetic route to this new type of 5-substituted isoxazole. The low yield of **8b** may be attributed in part to an acid–base reaction between the oxime dianion and the active hydrogen α to the carbonyl as shown in eq 2. This equilibrium may destroy some of the oxime



$$XC_6H_5\bar{C}{=}NO^- + RCH_2COOR' \rightleftharpoons XC_6H_4\bar{C}H{=}NO^- + R\bar{C}HCOOR' \quad (2)$$

dianion before the dianion could condense with the ester; also, formation of the ester monoanion should deactivate the ester toward attack by the oxime dianion.

Attempts to prepare isoxazoles *via* aroylation of possible dianions of the oximes of *m*-nitroacetophenone,

phenacyl chloride, and α-dimethylaminoacetophenone have been nonreproducible or unsuccessful. Isoxazoles, if formed, were in trace amounts and were contaminated with intractable tarry material.

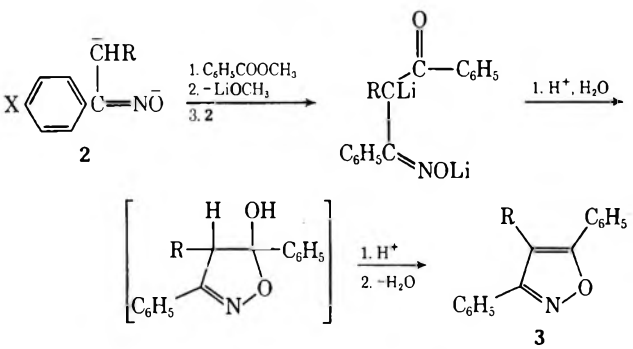
Table I summarizes the isoxazoles which were prepared during this investigation and gives significant data for each compound.

Discussion

The synthesis described in the present work has several advantages over previous methods: an unequivocal route to unsymmetrically substituted isoxazoles, readily available starting materials, compatibility with a variety of substituent groups, and a short, simple experimental procedure.

The formation of the oxime dianion by the action of *n*-butyllithium probably takes place by a stepwise process where protons of significantly different acidities are involved. In the case of a simple oxime of type **1**, the first equivalent of base removes the more acidic hydroxyl proton of the oxime, and the second equivalent of base removes a proton α to the oxime function. Evidence for the existence of such dianions has been obtained by alkylation of **2** with benzyl chloride and *n*-butyl bromide.[7] In both cases, the alkylation occurred at the more nucleophilic carbanionic site rather than at the oxygen site. The aroylation of the dilithio salt **2** (R = H) with methyl benzoate is similar to a Claisen aroylation and should involve a similar mechanism (see Scheme III).[8]

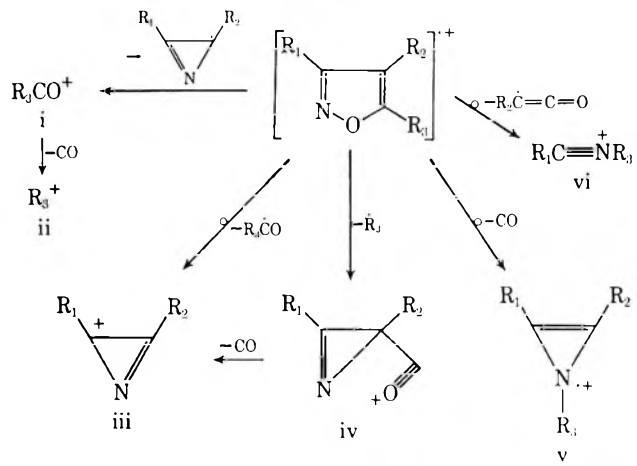
SCHEME III



In an attempt to find a readily available and simple method of identifying the isomers of a pair of unsymmetrically substituted 3,5-diarylisoxazoles, the mass spectra of many compounds prepared in this work were examined. In all cases an ion of relative intensity ≥50% arising from a fragmentation involving the 5 substituent was observed. Thus, mass spectrometry permits the identification of the isomer obtained and provides the needed check on the unequivocal nature of various isoxazole syntheses.

Our findings have been confirmed by the recent work of Bowie, Kallury, and coworkers[12,13] and Nakata and coworkers.[14,15] These investigators have correctly suggested on the basis of their work with alkylphenyl- and 3,5-diphenylisoxazoles[13,14] that the substituent at the 5 position of the isoxazole ring will be indicated by the presence of fragments arising from the loss of the substituent as a radical (M − R_3· peak),[12,15] or from cleavage of the heterocyclic ring to give an aroyl cation (R_3—C≡O$^+$)[12-15] (Scheme IV). The latter fragment, when present, will lose CO and give the aryl cation, R_3^+. The loss of a 5 substituent as a radical occurs in significant amounts only when a stable radical is formed (*e.g.*, the benzyl radical in **8b**). The M − R_3· ion then loses CO to give iii. The presence of metastable peaks for the latter fragmentation confirms the contribution of this pathway to the intensity of ion iii.

SCHEME IV[a]



[a] Looped arrows designate skeletal rearrangements during fragmentation to the indicated ion or ion radical.

In addition to these two primary fragmentation pathways, rearrangement–fragmentation involving the migration of the 5 substituent has been found to occur.[12,13] In the mass spectra of triarylisoxazoles **5a–c**, fragmentation involving the loss of phenyl ketene radical recently noted by Kallury and Bowie[13] has been confirmed. That the aromatic ring lost in the ketene radical is not the 5 substituent was demonstrated by retention of *para*-substituted phenyl groups of 5-*para*-substituted triarylisoxazoles in the ion vi.

Loss of stable neutral fragments was observed in systems where the 3 and 4 positions of the isoxazole ring were bridged by an aliphatic side chain (Scheme V).

In addition to the fragmentations involving cleavage of the isoxazole ring, fragmentations involving cleavage of aryl substituents were observed. These were consistent with previously reported cleavages, *e.g.*, loss of CH_3· in those compounds containing a methoxy group. Several doubly charged ions were present in the spectra of the compounds studied, and in all cases an ion corresponding to M^{2+} was observed. No attempt was made to describe the fragmentation pathways for such doubly charged species.

Table II summarizes the major fragmentations which were observed in the compounds studies.

Experimental Section

All analyses were performed by M-H-W Laboratories, Garden City, Mich. Infrared spectra were obtained on Perkin-Elmer Model 137 and 237 spectrometers. The nmr spectra were ob-

(12) J. H. Bowie, R. K. M. R. Kallury, and R. G. Cooks, *Aust. J. Chem.*, **22**, 563 (1969).

(13) B. K. Simons, R. K. M. R. Kallury, and J. H. Bowie, *Org. Mass Spectrom.*, **2**, 739 (1969).

(14) H. Nakata, H. Sakurai, H. Yoshizumi, and A. Tatematsu, *ibid.*, **1**, 199 (1968).

(15) H. Nakata, *et al.*, *ibid.*, **2**, 195 (1969).

TABLE II
MASS SPECTRAL DATA OF CERTAIN ISOXAZOLES[a]

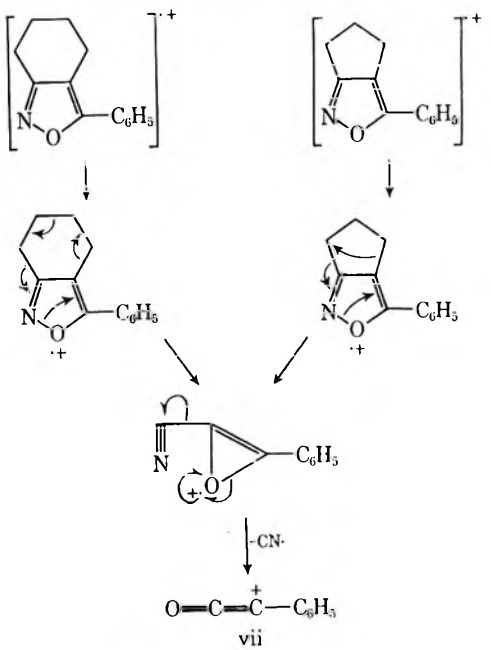
Compd no.	M+	M2+	i	ii	iii	iv	v	vi	vii
3b	255 (91)	127.5 (6.9)	139 (100)*	111 (19.5)*	116 (3)	144 (16)	227 (3.6)*		
3c	251 (63.2)	125.5 (6)	135 (100)*	107 (5.5)*	116 (1.5)	144 (2)	223 (0.3)*		
3d	255 (63)	127.5 (6.3)	105 (100)	77 (27)*	150 (2.5)	178 (5.5)	227 (1.5)*		
3e	251 (100)	125.5 (9.9)	105 (51)	77 (25)*	146 (4)	174 (8.5)	223 (0.6)*		
3f	285 (85)	142.5 (5.5)	135 (100)*	107 (4.5)*	150 (1.7)	178 (1.1)			
3g	285 (100)	142.5 (7)	139 (58)	111 (15)*	146 (31)	174 (9.2)			
5a	297 (100)	148.5 (3.9)	105 (92.2)	77 (33.3)*	192 (2.2)	220 (1.9)	269 (2.5)*	180 (33.3)*	
5b	331 (97)	166.5 (3.1)	139 (100)	111 (30.3)*	192 (2.7)	220 (1.6)	303 (3.2)*	214 (54.4)*	
5c	327 (95)	163.5 (5.3)	135 (100)	107 (5.7)*	192 (2.7)		229 (2.4)*	210 (52.5)*	
6b	277 (100)	138.5 (1.2)	135 (50.0)	107 (7.1)*	142 (1.5)		249 (5.1)*		
7a	185 (30.6)	92.5 (0.8)	105 (100)*[b]	77 (83.3)*	80 (3.1)	108 (2.2)	157 (4.4)		117 (8.3)
7b	199 (100)	99.5 (21.0)	105 (63.2)*[c]	77 (26.3)*	94 (21.1)	122 (1.8)	171 (1.1)*		117 (2.9)
8a	252 (100)	126 (10)	106 (33.4)	78 (26.2)*	146 (11.3)*[d]	174 (24.2)			
8b	235 (608)	117.5 (2.5)		91 (8.4)[e]	116 (8)*[d]	144 (100)*			

Other fragments[f]

3b: 258 (5.5) [M + 3]; 257 (30) [M + 2]; 256 (19.5) [M + 1]; 254 (14) [M − 1]; 141 (33) [i + 2]; 113 (7.5) [ii + 2]; 89 (5.5); 81 (9.5); 77 (7.7); 75 (5.9); 73 (5.2); 69 (18.3); 57 (7.3); 55 (7.0); 51 (6); 43 (7.4); 41 (7.3). **3c**: 252 (19) [M + 1]; 136 (11) [i + 1]; 92 (7.2) [ii − CH_3]; 77 (22.1). **3d**: 257 (22) [M + 2]; 256 (11) [M + 1]; 106 (7.6); 69 (5.5); 51 (5) [77 − C_2H_2]. **3e**: 252 (22) [M + 1]; 135 (48)*.[g] **3f**: 288 (5.2) [M + 3]; 287 (29.1) [M + 2]; 286 (15) [M + 1]; 136 (9.1) [i + 1]: 92 (6.2) [ii − CH_3]; 81 (5); 77 (10); 69 (11). **3g**: 288 (6) [M + 3]; 287 (33) [M + 2]; 286 (19) [M + 1]; 270 (6.8) [M − CH_3]; 149 (16); 141 (17) [i + 2]; 138 (7.5); 137 (10); 97 (5.7); 95 (6.2); 83 (7.5); 82 (6); 81 (19); 73 (9.5); 71 (9.5); 70 (6.5); 69 (48); 68 (6.5); 67 (5); 60 (8.5); 57 (17); 56 (5.5); 55 (14); 43 (16.5); 41 (17.6). **5a**: 298 (24.2) [M + 1]; 166 (6.3); 165 (14.5); 106 (7.1); 89 (9.4); 51 (5.5) [ii − C_2H_2]. **5b**: 334 (8.4) [M + 3]; 333 (34.9) [M + 2]; 332 (25.4) [M + 1]; 216 (17) [vi + 2]; 165 (19.1); 148 (5.5); 141 (31.7) [i + 2]; 140 (7.9); 113 (21.4) [ii + 2]; 112 (7.9); 89 (13.9); 51 (5.2). **5c**: 328 (24) [M + 1]; 211 (7.9) [vi + 1]; 196 (5.8); 181 (5.3); 136 (9.5) [i + 1]; 92 (7.4); 89 (7.4); 78 (13.1); 77 (15.3). **6a**: 278 (13.7) [M + 1]; 262 (7.1) [M − CH_3]*; 248 (23) [M − HCO]; 234 (11.1) [M − (CH_3 + CO)]; 233 (5.1) [M − (HCO + CH_3)]; 218 (9.1); 133 (6.0); 92 (9.4) [ii − CH_3]; 89 (5.8); 77 (14.6). **7a**: 186 (4.9) [M + 1]; 156 (14.7) [M − HCO]; 130 (9.3); 129 (12.8); 115 (9.4); 106 (8) [i + 1]; 103 (13.3); 78 (8.6) [ii + 1]; 53 (5.6); 52 (6.1); 51 (30.6) [ii − C_2H_2]; 50 (7.5); 42 (8.3). **7b**: 200 (14.7) [M + 1]; 143 (7.1) [M − C_4H_8]; 106 (5.5) [i + 1]; 104 (5.5); 91 (21); 51 (6.3) [ii − CH_2]$_2$. **8a**: 253 (17.5) [M + 1]; 237 (21) [M − CH_3]*; 221 (5), [M − CH_3O]*; 51 (6.3) [ii − HCN). **8b**: 236 (18.4) [M + 1]; 145 (12.5) [iv + 1]; 89 (4.1) [iii − HCN]*; 77 (16); 76 (10)

[a] Tabulated are *m/e* (relative intensity) for the molecular ion, doubly charged molecular ion, and ions corresponding to general structures i–vii in Schemes IV and V. Asterisks indicate fragmentations for which metastable peaks were observed. All observed metastable peaks agree to ±0.2 of the calculated value. [b] Metastable peaks at 77.2 and 51.4 indicate that two fragmentations 143 → 105 and 185 → 105 contribute to the intensity of this ion fragment. [c] Metastable peak at 77.1 indicates that fragmentation 143 → 105 contributes to the intensity of the 105 ion peak. [d] Metastable peaks indicate that these fragments arise in part that iv by loss of CO or CO. [e] This fragment shows no evidence of arising from fragmentation, Scheme IV. [f] Ions of relative intensity ≥5%. Data which are in brackets indicate postulated origin. Since high resolution was not employed except for select cases, ions of other elemental composition than those indicated may contribute to the reported peak. [g] High resolution indicates that this ion has the composition $C_8H_7O_2$ (mol wt calcd 135.0445, found 135.0449); metastable peak indicates that it arises from the molecular ion.

SCHEME V



tained using a Varian A-60 nmr spectrometer using trifluoroacetic acid as a solvent, and shifts are reported in parts per million downfield (δ) from an internal tetramethylsilane (TMS) standard. Mass spectra were taken at the Research Triangle Institute for Mass Spectrometry, Durham, N. C., on an MS-902 mass spectrometer.[16] Melting points were taken on samples in open capillary tubes in a Thomas–Hoover melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately before use. The *n*-butyllithium was obtained from Alfa Inorganics, Inc., Beverly, Mass., and was used as supplied.

General Procedure for Conversion of an Oxime to Its Dilithio Salt.—To a stirred solution of 0.025 mol of oxime in 100 ml of THF, which was cooled to 0° under a nitrogen atmosphere, was added during 5 min 22.5 ml (0.05 mol) of 2.25 *M* *n*-butyllithium. After 30 min, the solution was assumed to contain 0.025 mol of dilithio salt, which was condensed with an ester as described below.

General Procedure for Aroylation[17] of Dilithio Salt Followed by Acid Cyclization to Form Isoxazole.—A 0.0125-mol sample of the ester dissolved in 15 ml of THF was added during 5 min to a solution containing 0.025 mol of dilithio salt (prepared as described above). After stirring at 0° for 15 min, the mixture was neutralized with 100 ml of 3 *N* hydrochloric acid. The mixture was then heated at reflux temperature for 1 hr and cooled, and

(16) The authors thank Dr. David Rosenthal for the mass spectral determinations, which were done at the Research Triangle Mass Spectrometry Center supported by Special Facility Grant No. Fr-00330-01, National Institutes of Health.

(17) Condensations of the oxime dianion with ethyl phenyl acetate followed by acid cyclization were carried out using this procedure.

the layers were separated. The aqueous layer was neutralized with sodium bicarbonate and extracted with three 50-ml portions of ether. The combined ether extracts were concentrated at reduced pressure on the steam bath.[18] If the residue contained a mixture of solid and an oil, it was washed with 10 ml of cold (0°) methanol and filtered immediately. If a solid was not formed, 5–10 ml of methanol was added and crystallization occurred upon refrigeration of the mixture. Recrystallization was effected with ethanol or benzene (see Table I).

(18) Conveniently, crystallization was found to be hastened if the ether extracts were not dried before removal of excess solvents, especially when *p*-methoxyaryl isoxazoles were synthesized.

Registry No.—**3b**, 1148-87-4; **3c**, 3672-51-3; **3d**, 24097-17-4; **3e**, 3672-52-4; **3f**, 24097-19-6; **3g**, 24097-20-9; **5a**, 22020-72-0; **5b**, 24097-22-1; **5c**, 24097-23-2; **6a**, 24097-24-3; **6b**, 24097-25-4; **7a**, 24097-26-5; **7b**, 24097-27-6; **8a**, 24162-37-0; **8b**, 18753-56-5.

Racemization of Amino Acid Derivatives. Rate of Racemization and Peptide Bond Formation of Cysteine Active Esters[1]

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It is demonstrated that N-carbobenzoxy-S-benzyl-L-cysteine active esters do not racemize *via* a "β-elimination–readdition" mechanism in the presence of triethylamine. Racemization and coupling rate constants of several N-carbobenzoxy-S-benzyl-L-cysteine esters are reported. The rate data indicate that (a) the required coupling time in some cases is considerably less than usually used in preparative work and (b) an N-protected amino acid containing a fast-coupling active ester can be joined with a slowly reacting active ester to yield optically pure carboxyl-activated intermediates which are useful for the preparation of high molecular weight sequential polypeptides. Comparison and evaluation of the coupling and racemization rate data allows selection of the "best suited" active ester for peptide bond formation under the conditions employed.

The most important problem in peptide synthesis is to avoid racemization. Racemization through an oxazolone[2] intermediate has been studied in detail and is well understood. However, some amino acid derivatives, where oxazolone formation is believed to be absent, have been found to racemize in the presence of base.[3] It has been suggested that racemization of these derivatives proceeds through α-hydrogen abstraction.[3] The unusual facility with which cysteine[4] and serine[5] derivatives racemize has been attributed to a "β-elimination–readdition" mechanism.[6] Even N-carbobenzoxy- and N-*t*-butoxycarbonyl-S-benzyl-L-cysteine active esters racemize in the presence of triethylamine.[3a,c]

In this paper we report studies on the mechanism of racemization and the comparison of the rates of racemization and peptide bond formation of N-carbobenzoxy-S-benzyl-L-cysteine active esters as a model for peptide synthesis. These studies led to important conclusions concerning the choice of an active ester for the synthesis of oligopeptides as well as high molecular weight sequential polypeptides.

Evaluation of the β-Elimination–Readdition Mechanism.[6]—The racemization of N-carbobenzoxy-S-benzyl-L-cysteine pentachlorophenyl ester with excess triethylamine was studied in the presence of benzyl mercaptan-^{35}S. The partially racemized active ester was isolated without any incorporation of radioactive sulfur.[7] On the other hand, racemization of N-carbobenzoxy-S-benzyl-L-cysteine *p*-nitrophenyl ester under identical conditions resulted in partially racemized N-carbobenzoxy-S-benzylcysteine thiobenzyl ester[8] (77% yield) which contained one equivalent of radioactive sulfur. The position of the sulfur-35 was established by hydrazinolysis of the thiobenzyl ester. The corresponding hydrazide showed complete absence of the incorporated sulfur-35.

These experiments clearly confirm that β-elimination–readdition is not the mechanism for the racemization of N-carbobenzoxy-S-benzyl-L-cysteine active esters under these basic conditions. This result leads one to conclude that racemization of cysteine derivatives proceeds through abstraction of the α hydrogen.

Racemization of N-Carbobenzoxy-S-benzyl-L-cysteine Active Esters.—The racemization of the active esters listed in Table I was carried out in tetrahydrofuran solution in the presence of triethylamine under strictly anhydrous conditions. When anhydrous solvents were used but manipulations were not carried out in a drybox, the racemization of some of the active esters was accompanied by hydrolysis which usually

(1) Part III of a series on racemization studies of amino acid derivatives. For parts I and II see ref 6.

(2) (a) M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, **86**, 2918 (1964); (b) M. Goodman and K. C. Steuben, *J. Org. Chem.*, **27**, 3409 (1962). (c) M. W. Williams and G. T. Young, "Peptides," Proceedings of the Fifth European Peptide Symposium, Oxford, 1962, G. T. Young, Ed., Pergamon, London, 1963, p 119; (d) G. T. Young and I. Antonovics, *Acta Chim. (Budapest)*, **44**, 43 (1968); (e) M. Goodman and W. J. McGahren, *J. Amer. Chem. Soc.*, **87**, 3028 (1965); (f) M. Goodman and W. J. McGahren, *Tetrahedron*, **23**, 2031 (1967); (g) J. Kovacs, L. Kisfaludy, M. Q. Ceprini, and R. H. Johnson, *ibid.*, **25**, 2555 (1969).

(3) (a) G. W. Anderson, F. M. Callahan, and J. E. Zimmerman, *Acta Chim.* (Budapest), **44**, 51 (1965); (b) B. Liberek and A. Michalik, *ibid.*, **44**, 71 (1965); (c) B. Liberek, *Tetrahedron Lett.*, 925 (1963).

(4) (a) J. A. MacLaren, W. E. Savige, and J. M. Swan, *Aust. J. Chem.*, **11**, 345 (1958); (b) M. Bodanszky and A. Bodanszky, *Chem. Commun.*, 591 (1967).

(5) (a) E. Schnabel, *Z. Physiol. Chem.*, **314**, 114 (1959); (b) Z. Bohak and E. Katchalski, *Biochemistry*, **2**, 228 (1963).

(6) Preliminary communications: J. Kovacs, G. L. Mayers, R. H. Johnson, and U. R. Ghatak, *Chem. Commun.*, 1066 (1968); J. Kovacs, G. L. Mayers, R. H. Johnson, R. E. Cover, and U. R. Ghatak, *ibid.*, 53 (1970).

(7) The readdition of benzyl mercaptan to N-carbobenzoxydehydroalanine pentachlorophenyl ester yielded racemic N-carbobenzoxy-S-benzylcysteine pentachlorophenyl ester. On the other hand, N-carbobenzoxydehydroalanine *p*-nitrophenyl ester on reaction with 1 equiv of benzyl mercaptan under similar conditions yielded a complex mixture, two components of which are N-carbobenzoxy-S-benzyl-DL-cysteine *p*-nitrophenyl ester and N-carbobenzoxy-S-benzyl-DL-cysteine thiobenzyl ester. When the above reaction was run with 2 equiv of benzyl mercaptan, N-carbobenzoxy-S-benzyl-DL-cysteine thiobenzyl ester was isolated in high yield.

(8) This unexpected difference in the behavior between the *p*-nitrophenyl ester and the pentachlorophenyl ester in ester exchange reaction with benzyl mercaptan led to the investigation of the reaction of several other active esters with benzyl mercaptan. The data in Table IV suggest that steric effects may play a role in this ester exchange reaction.

manifested itself both as a residual rotation which remained practically constant for a considerable length of time and by diminution of the active ester carbonyl absorption in the infrared spectra.[9] Table I gives the second-order rate constants which were determined for the racemization of N-carbobenzoxy-S-benzyl-L-cysteine active esters.[10] These values were shown to be true second-order rate constants by carrying out experiments at 1, 7, and 35 equiv of triethylamine/mol of ester.

TABLE I

THE SECOND-ORDER RACEMIZATION RATE CONSTANTS FOR THE REACTION OF CARBOBENZOXY-S-BENZYL-L-CYSTEINE ACTIVE ESTERS[10] WITH TRIETHYLAMINE[a,b]

R of Z-Cys-R (BZL)	$k_{rac} \times 10^4$, M^{-1} sec^{-1}
-OSu[c]	48.8 ± 2
-OPFP[c]	33.0 ± 6
-ODNP (2,4)[c]	29.6 ± 2
-ODNP (2,6)[c]	29.0 ± 2
-OTCP (2,4,5)[d]	4.88 ± 0.6
-OPCP[c]	4.14 ± 0.2
-ONP[c]	3.94 ± 0.3
-OTCP (2,4,6)[c]	0.80 ± 0.05
-OPBP[c]	0.414 ± 0.02
-OTBP (2,4,6)[c]	0.1718 ± 0.001
-OPh[c]	0.0972 ± 0.002
-OEt[c,e]	No racemization[f]
-NHCH$_2$CO$_2$Et	No racemization[f]

[a] 23 ± 1°, in tetrahydrofuran. [b] The concentration range of triethylamine was 0.22–0.36 *M*. [c] The average of two experiments. [d] The average of four experiments. [e] 3.6 equiv of triethylamine. [f] Up to 7 days.

Aminolysis Rate Studies of N-Carbobenzoxy-S-benzyl-L-cysteine Active Esters.—The second-order rate constants for peptide bond formation between N-carbobenzoxy-S-benzyl-L-cysteine active esters and L-valine methyl ester are reported in Table II. L-Valine methyl ester was chosen for these reactions, since other methyl esters such as glycine and phenylalanine react too fast to be followed by the infrared techniques employed. Column 3 in Table II indicates the time required for 90% completion of the coupling reaction. The reaction between the phenyl ester and valine methyl ester was too slow to follow; the pentabromophenyl ester was insoluble in the solvent medium. The "activity" of esters in Table II is practically parallel with the rates of racemization recorded in Table I with the exception of the hydroxysuccinimide ester.

TABLE II

THE SECOND-ORDER COUPLING RATE CONSTANTS FOR THE REACTION OF N-CARBOBENZOXY-S-BENZYL-L-CYSTEINE ACTIVE ESTERS WITH VALINE METHYL ESTER[a]

R of Z-Cys-R (BZL)	$k_0 \times 10^2$, M^{-1} sec^{-1}	90% reaction time, min
-OPFP[b,d]	40.4 ± 9	2.9
-ODNP (2,4)[b,d]	18.4 ± 3	6.3
-OSu[b,d]	5.44 ± 0.7	21
-ODNP (2,6)[b,e]	1.73 ± 0.2	67
-OPCP[c,f]	1.72 ± 0.2	62[g]
OTCP (2,4,5)[b,f]	0.298 ± 0.03	385
-ONP[b,f]	0.105 ± 0.01	1088
-OTCP (2,4,6)[b,f]	0.0626 ± 0.002	1856
-OTBP (2,4,6)[b,f]	0.0215 ± 0.006	5310

[a] 23 ± 1°, in tetrahydrofuran. [b] The concentration of the active ester and valine methyl ester was 0.13 *M*. [c] The concentration of this ester and valine methyl ester was 0.0845 *M*. [d] The average of four experiments. [e] The average of three experiments. [f] The average of two experiments. [g] This value is based on an initial concentration of 0.0845 *M*.

As is evident from these data, even for the sterically hindered valine methyl ester, the required coupling time, in some cases, is considerably less than that usually used in preparative work. For example, from the reaction of N-carbobenzoxy-S-benzyl-L-cysteine pentafluorophenyl ester and valine methyl ester, the dipeptide was isolated in 90% yield after 5 min of reaction time. Peptide formation employing minimum required coupling time would lessen the danger of racemization. The rate data of Table II also indicate that a rapidly reacting N-protected active ester, such as N-carbobenzoxy-S-benzyl-L-cysteine pentafluorophenyl ester, may be coupled with slowly reacting amino acid active ester such as glycine *p*-nitrophenyl ester with a negligible amount of self-condensation of the latter. The N-protected dipeptide *p*-nitrophenyl ester was isolated in good yield in spite of the fact that the glycine active ester is expected to react the fastest in self-condensation. This variation of the "backing-off" procedure[11] would be very important for preparing intermediates for optically pure sequential polypeptides.[2g,12]

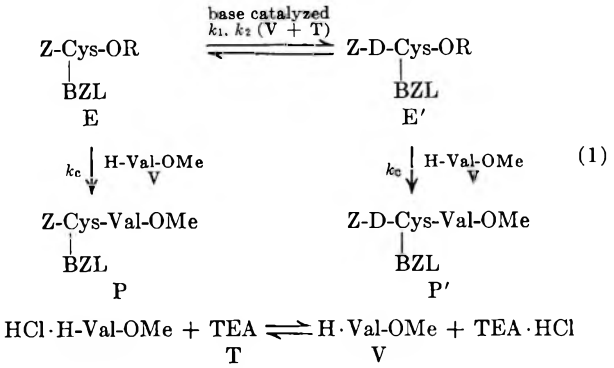
Rate Factors Influencing the Optical Purity of N-Carbobenzoxy Amino Acid Esters during Peptide Bond Formation.—Since a desired feature for peptide synthesis is racemization-free amide bond formation, a favorable ratio between coupling and racemization rates must exist if high molecular weight, optically pure polypeptides are to be obtained. The following general scheme was used to derive equations from which the optical purity of a peptide could be evaluated where

(9) In the study of the racemization of N-carbobenzoxy-S-benzyl-L-cysteine *p*-nitrophenyl ester, in which anhydrous tetrahydrofuran was used without manipulation being carried out in a drybox, atmospheric moisture was absorbed by the solvent. This led to hydrolysis and from the solution partially racemized N-carbobenzoxy-S-benzylcysteine was isolated. Under similar conditions a more striking example was observed during the racemization of N-carbobenzoxy-L-phenylalanine *p*-nitrophenyl ester in chloroform solution (*c* 3.8) in the presence of 7 equiv of triethylamine; the apparent specific rotation changed from −7.4 to 12.1; N-carbobenzoxy-L-phenylalanine had a specific rotation of $[\alpha]^{23}D$ 87.6° (*c* 3.0, chloroform containing 7 equiv of triethylamine).

(10) The following abbreviations have been used: Z = carbobenzoxy; BZL = benzyl; Su = N-hydroxysuccinimidyl; PFP = pentafluorophenyl; DNP (2,4) = 2,4-dinitrophenyl; DNP (2,6) = 2,6-dinitrophenyl; TCP (2,4,5) = 2,4,5-trichlorophenyl; PCP = pentachlorophenyl; NP = *p*-nitrophenyl; TCP (2,4,6) = 2,4,6-trichlorophenyl; PBP = pentabromophenyl; TBP (2,4,6) = 2,4,6-tribromophenyl. The known esters listed below were prepared by the method described for the pentachlorophenyl ester. N-hydroxysuccinimide ester, mp 90–91°, $[\alpha]^{22}D$ −58.5° (*c* 1.8, dioxane) {lit. mp 91–92°, $[\alpha]D$ −58° ± 2.9° (*c* 1.746, dioxane), private communication from Dr. G. W. Anderson}; pentafluorophenyl ester, mp 83–84°, $[\alpha]D$ −40.0° (*c* 2.05, tetrahydrofuran), prepared in this laboratory by J. Roberts; *p*-nitrophenyl ester, mp 94–95°, $[\alpha]^{22}D$ −43.6° (*c* 1, dimethylformamide) {lit. mp 93–94°, $[\alpha]^{22}D$ −42° (*c* 1, dimethylformamide), M. Bodanszky and V. du Vigneaud, *J. Amer. Chem. Soc.*, **81**, 2504 (1959)}; 2,4,6-trichlorophenyl ester, mp 110–111°, $[\alpha]^{23}D$ −61.0° (*c* 1, ethyl acetate {lit. mp 111–112°, $[\alpha]^{20}D$ −62° ± 2° (*c* 1, ethyl acetate), G. Kupryszewski, *Rocz. Chem.*, **37**, 593 (1963)}; phenyl ester, mp 100–101°, $[\alpha]^{23}D$ −10.9° (*c* 2, chloroform) {(lit. mp 100–102°, $[\alpha]D$ −11.0° (*c* 1, chloroform), G. Blotnz, J. Biernat, and E. Taschner, *Justus Liebigs Ann. Chem.*, **663**, 194 (1963)}.

(11) M. Goodman and K. C. Steuben, *J. Amer. Chem. Soc.*, **81**, 3980 (1959).

(12) (a) J. Kovacs, R. Giannotti and A. Kapoor, *ibid.*, **88**, 2282 (1966); (b) J. Kovacs, L. Kisfaludy, M. Q. Ceprini, *ibid.*, **89**, 183 (1967).



(1)

E is the starting ester, E′ is its enantiomer, P is the optically pure peptide, P′ is the undesired diastereomer, V is the coupling base, T is a base added to release V from its acid salt, k_c is the second-order coupling rate constant, and k_1 and k_2 are the interconversion rate constants of E and E′ for V and T, respectively.

The following assumption was made in deriving the rate expressions given below. The coupling rate constant, k_c, is identical for reactions of both E and E′.

$$\frac{dC_{E'}}{dt} = -(k_c + k_1)C_{E'}C_V - k_2C_{E'}C_T + k_2C_EC_T + k_1C_EC_V \quad (2)$$

$$\frac{dC_P}{dt} = k_cC_EC_V \quad (3)$$

$$\frac{dC_{P'}}{dt} = k_cC_{E'}C_V \quad (4)$$

from which one may write

$$\left(\frac{C_P}{C_{P'}}\right)_\infty = \frac{\int_0^\infty C_EC_V dt}{\int_0^\infty C_{E'}C_V dt} \quad (5)$$

Making the steady-state assumption for E′, solving for $(C_{E'}C_V)$, and substituting into eq 5, the product ratio becomes

$$\left(\frac{C_P}{C_{P'}}\right)_\infty = \frac{(k_c + k_1)\int_0^\infty C_EC_V dt}{\int_0^\infty (k_1C_EC_V + k_2(C_E - C_{E'})C_T)\,dt} \quad (6)$$

but, since in the steady state, $C_E \gg C_{E'}$, we may write

$$\left(\frac{C_P}{C_{P'}}\right)_\infty = \frac{(k_c + k_1)\int_0^\infty C_EC_V dt}{\int_0^\infty (k_1C_EC_V + k_2C_EC_T)dt} \quad (7)$$

If one further assumes that (a) equimolar amounts of T and the acid salt of V are present at the start of the reaction in a homogenous system and (b) T and V are in equilibrium throughout the reaction, then

$$C_T = KC_V \quad (8)$$

Substituting for C_T from eq 8 into eq 7 gives

$$\left(\frac{C_P}{C_{P'}}\right)_\infty = \frac{k_c + k_1}{k_1 + k_2K} \quad (9)$$

The values of $(C_P/C_{P'})_\infty$ expressed in eq 7 and 9 represent the maximum amount of the undesired diastereomer that could form under the experimental conditions assumed.

In the case where racemization is rapid relative to coupling, and if the coupling rate constants differ for the L and D active esters,[13] eq 9 becomes

$$\left(\frac{C_P}{C_{P'}}\right)_\infty = \frac{k_c}{k_{c'}} \quad (10)$$

where k_c and k_c' are the coupling rate constants for esters E and E′. In our systems where racemization is slow relative to coupling, large differences between k_c and k_c' should not affect the validity of our conclusions.

In the model system studied, namely, the coupling of N-carbobenzoxy-S-benzyl-L-cysteine active esters with L-valine methyl ester hydrochloride in the presence of triethylamine in tetrahydrofuran solution at room temperature, the values of $(C_P/C_{P'})_\infty$ can be evaluated from the rate data presented in Tables I and II. The value that was used for k_2 in this evaluation was $^1/_2k_{rac}$ given in Table I. Inasmuch as experimental results show that even an excess of valine methyl ester causes no racemization during active ester coupling, k_1 in eq 9 may be neglected. Since K is a constant depending upon the reaction system, the ratios of k_c/k_2, which are presented in Table III indicate the relative extents to which these active esters are susceptible to racemization during coupling.

TABLE III
RATIO OF COUPLING AND RACEMIZATION RATES

R of Z-Cys-R (BZL)	k_c/k_2	$(C_P/C_{P'})_\infty$
-OPFP	245	62
-ODNP (2,4)	124	35
-OPCP	83	25
-OTBP (2,4,6)	25	11
-OSu	22	11
-OTCP (2,4,6)	16	9
-OTCP (2,4,5)	12	7.1
-ODNP (2,6)	12	6.7
-ONP	5.3	4.2

The values tabulated for $(C_P/C_{P'})_\infty$ in Table III were obtained from analog computer simulations for the coupling system containing 1 equiv of valine methyl ester hydrochloride, 1 equiv of N-carbobenzoxy-S-benzyl-L-cysteine active ester, and 2 equiv of triethylamine. Similar conditions are commonly present[12,14] in the synthesis of high molecular weight sequential polypeptides.

Standard analog programming techniques were used[15] employing the experimentally determined rate constants for each system. The initial concentrations for the active ester, the free valine methyl ester, and the triethylamine were all taken as 0.129 M. These initial conditions assume that triethylamine instantaneously releases the free valine methyl ester from its acid salt. The computer simulations permit the evaluation of the product ratios, $(C_P/C_{P'})_\infty$, without making the steady-state assumption.

As can be seen from Table III, the computer-derived product ratios parallel the k_c/k_2 ratios derived using the steady-state assumption; however, these ratios are not linearly related. This nonlinearity could be due to the fact that the steady-state assumption may be invalid for systems with small k_c/k_2 ratios and the fact that the two sets of computations are based on disparate assumptions about the nature of the equilibrium between the two bases.

(13) W. Steglich, D. Mayer, X. Barocio De La Lama, H. Tanner, and F. Weygand, "Peptides," Proceedings of the Eighth European Peptide Symposium, Noordwijk, The Netherlands, Sept 1966, North-Holland Publishing Co., Amsterdam, 1967, p 67.

(14) J. Kovacs, G. N. Schmit, and U. R. Ghatak, *Biopolymers*, **6**, 817 (1968).

(15) A. S. Jackson, "Analog Computations," McGraw-Hill Book Co., New York, N. Y., 1960.

Since optimum synthesis conditions are those in which $(C_{P'})_\infty$ is minimized (racemization is small), the most desirable active ester would be one in which the product ratio is largest. Where racemization is critical, such as cysteine, these data indicate that the *p*-nitrophenyl ester, one of the active esters most frequently used in coupling, would produce more of the undesired diastereomer under these conditions than any of the other esters investigated.

Experimental Section

All melting points are uncorrected and were determined in a Thomas–Hoover melting point apparatus. The kinetics of racemization were studied either on the Rudolph photoelectric polarimeter, Model 200S-340-8006, or on the Cary Model 60 recording spectropolarimeter. Coupling kinetics were studied on a Beckman Model IR-8 spectrophotometer. All kinetic studies were done in a constant temperature room (23 ± 1°); no other thermostatting was used. All computer data were obtained from two slaved EAI TR-20 analog computers. Radioactive samples were counted on a Tri-Carb liquid scintillation spectrometer (Packard Model 2002).

Solvents and Reagents.—Tetrahydrofuran was purified by refluxing for 3 days over solid potassium hydroxide, then distilled. The distillate was refluxed over lithium aluminum hydride for one day, followed by distillation. The purified material was then stored over molecular sieves. Reagent grade triethylamine was converted to its hydrochloride salt, recrystallized from absolute ethanol, then liberated from its salt with aqueous sodium hydroxide, dried over solid potassium hydroxide, and distilled from sodium under nitrogen. The purified material was stored over sodium. The valine methyl ester was twice distilled under vacuum and stored in the freezer.

Preparation N-Carbobenzoxy-S-benzyl-L-cysteine Pentachlorophenyl Ester.—Dicyclohexylcarbodiimide (4.12 g, 20 mmol) and pentachlorophenol (5.33 g, 20 mmol) were dissolved in 100 ml of anhydrous ethyl acetate at room temperature. The solution was cooled to 0° in an ice bath and 6.9 g (20 mmol) of N-carbobenzoxy-S-benzyl-L-cysteine were added. The reaction mixture was stirred at 0° for 1 hr and then at room temperature for 1 hr. The dicyclohexylurea (DCU) was removed by filtration and washed with dioxane. The ethyl acetate and dioxane filtrates were combined and the solvent was removed *in vacuo*. The residue was redissolved in dioxane and filtered to remove residual DCU. The dioxane was removed *in vacuo;* the crude yield was 10.6 g (89%). It was recrystallized from dimethylformamide–methanol, yield 8.0 g (67%), mp 171–172°, (lit.[16] mp 171–172°), $[\alpha]^{23}D$ −38.9° (*c* 0.7, chloroform). The ir spectrum showed the characteristic active ester peak at 5.6 μ (KBr).

Anal. Calcd for $C_{24}H_{18}NO_4Cl_5$: C, 48.55; H, 3.06; N, 2.36; S, 5.40; Cl, 29.86. Found: C, 48.26; H, 2.87; N, 2.32; S, 5.56; Cl, 30.31.

The above procedure was used for the preparation of the other active esters described below.

N-Carbobenzoxydehydroalanine Pentachlorophenyl Ester.—The crude semisolid product was triturated with petroleum ether (bp 40–60°) and filtered giving a white solid, mp 129–131° (62% yield). It was recrystallized from ethyl acetate, mp 131–133°, λ_{KBr} 5.68 μ (active ester).

Anal. Calcd for $C_{17}H_{10}NO_4Cl_5$: C, 43.49; H, 2.15; N, 2.98; Cl, 37.75. Found: C, 43.45; H, 2.03; N, 2.86; Cl, 37.33.

N-Carbobenzoxydehydroalanine *p*-Nitrophenyl Ester.—This crude oily product was chromatographed on a column of silica gel (i.d. 2.5 cm, height 33 cm) using benzene–petroleum ether (bp 40–60°). The first two fractions afforded an oil which crystallized on standing. The solid was triturated with pentane and filtered, mp 66–69° (yield 32%). The material was recrystallized from ether–pentane, mp 70–71°, λ_{KBr} 5.72 μ (active ester).

Anal. Calcd for $C_{17}H_{14}N_2O_6$: C, 59.66; H, 4.12; N, 8.19. Found: C, 59.76; H, 4.47; N, 8.28.

N-Carbobenzoxy-S-benzyl-L-cysteine Pentabromophenyl Ester.—The crude ester melted at 189–191° (yield 93%). The ester was recrystallized from dimethylformamide–methanol, mp 196–197°, $[\alpha]^{22}D$ −40.9° (*c* 2.04, tetrahydrofuran), λ_{KBr} 5.65 μ (active ester).

Anal. Calcd for $C_{24}H_{18}NO_4SBr_5$: C, 35.43; H, 2.20; N, 1.72; S, 3.93; Br, 48.96. Found: C, 35.43; H, 2.20; N, 2.01; S, 3.69; Br, 48.21.

N-Carbobenzoxy-S-benzyl-L-cysteine 2,4,6-Tribromophenyl Ester.—The yield was 80%; recrystallization from ethyl acetate–pentane gave needles, mp 119–120°, $[\alpha]^{25}D$ −48.6° (*c* 3.24, tetrahydrofuran), λ_{KBr} −5.62 μ (active ester).

Anal. Calcd for $C_{24}H_{20}NO_4SBr_3$: C, 43.79; H, 3.06; N, 2.13; S, 4.87; Br, 36.42. Found: C, 43.96; H, 2.98; N, 2.05; S, 4.90; Br, 36.30.

N-Carbobenzoxy-S-benzyl-L-cysteine 2,4,5-Trichlorophenyl Ester.—The yield was 92%, mp 92–93°. It was recrystallized from ethyl acetate–hexane, mp 92–93°, $[\alpha]^{22}D$ −43.9° (*c* 2.5, tetrahydrofuran), λ_{KBr} 5.62 μ (active ester).

Anal. Calcd for $C_{24}H_{20}NO_4SCl_3$: C, 54.92; H, 3.84; N, 2.67; S, 6.11; Cl, 20.26. Found: C, 55.08; H, 4.15; N, 2.54; S, 5.77; Cl, 20.52.

N-Carbobenzoxy-S-benzyl-L-cysteine 2,4-Dinitrophenyl Ester.—The yield was 73%, mp 93–95°. It was recrystallized from absolute ethanol, mp 98–100°, $[\alpha]^{25}D$ −61.5° (*c* 2.54, tetrahydrofuran), λ_{KBr} 5.62 μ (active ester).

Anal. Calcd for $C_{24}H_{21}N_3O_8S$: C, 56.36; H, 4.14; N, 8.22; S, 6.27. Found: C, 56.65; H, 4.56; N, 8.31; S, 6.31.

N-Carbobenzoxy-S-benzyl-L-cysteine 2,6-Dinitrophenyl Ester.—The yield was 73%, mp 102–104°. It was recrystallized from absolute ethanol, mp 107–108°, $[\alpha]^{23}D$ −103.8° (*c* 1.8, tetrahydrofuran), λ_{KBr} 5.58 μ (active ester).

Anal. Calcd for $C_{24}H_{21}N_3O_8S$: C, 56.36; H, 4.14; N, 8.22; S, 6.27. Found: C, 56.58; H, 4.18; N, 8.30; S, 6.41.

N-Carbobenzoxy-S-benzyl-L-cysteine Thiobenzyl Ester.—The crude oily product was crystallized from methanol–water, mp 73–75° (recrystallization from ethanol did not change the melting point), yield 45%, $[\alpha]^{22}D$ −94.8° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{25}H_{25}NO_3S_2$: C, 66.49; H, 5.58; N, 3.10; S, 14.20. Found: C, 66.70; H, 5.59; N, 32.1; S, 13.85.

Racemization of N-Carbobenzoxy-S-benzyl-L-cysteine Pentachlorophenyl Ester in the Presence of Benzyl Mercaptan-^{35}S.—N-Carbobenzoxy-S-benzyl-L-cysteine pentachlorophenyl ester (891 mg, 1.5 mmol) was dissolved in 30 ml of anhydrous chloroform. Benzyl mercaptan-^{35}S (0.176 ml, 1.55 mmol) (the benzyl mercaptan-^{35}S was obtained from Nuclear Chicago and diluted with unlabeled benzyl mercaptan; the activity was 3300 cpm/μmol) and triethylamine (1.5 ml, 10.3 mmol) were added and the mixture was stirred at room temperature for 90 min. The triethylamine was neutralized with 1 ml of concentrated hydrochloric acid. The chloroform solution was washed with water until neutral and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo*. The residue was triturated with pentane and filtered. The yield was 775 mg (87%), mp 164–166°. Recrystallization of a small portion from ethyl acetate raised the melting point to 168–169°, $[\alpha]^{25}D$ −0.8° (*c* 2, chloroform).

Anal. Calcd for $C_{24}H_{18}NO_4SCl_5$: C, 48.55; H, 3.06; N, 2.36. Found: C, 48.83; H, 3.36; N, 2.50.

The recrystallized pentachlorophenyl ester (10 mg) was dissolved in 10 ml of toluene (scintillation grade); this solution was used to prepare samples for scintillation counting. The scintillator solution was *p*-bis[2-(5-phenyloxazolyl)]benzene (0.4%) and 2,5-diphenyloxazole (0.005%) made up in scintillation grade toluene. The counting showed the active ester had 3.6 ± 2 cpm/μmol.

Racemization of N-Carbobenzoxy-S-benzyl-L-cysteine *p*-Nitrophenyl Ester in the Presence of Benzyl Mercaptan-S^{35}.—N-Carbobenzoxy-S-benzyl-L-cysteine *p*-nitrophenyl ester (1.4 g, 3 mmol) was dissolved in 60 ml of chloroform. Benzyl mercaptan-^{35}S (activity 3300 cpm/μmol, 0.351 ml, 3 mmol) and triethylamine (3 ml, 21.5 mmol) were added and the mixture was stirred at room temperature for 90 min. The triethylamine was neutralized with 2 ml of concentrated hydrochloric acid. The chloroform solution was washed with water until neutral and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* at room temperature. The residue was an oil, which was dissolved in ethyl acetate and precipitated with pentane to yield five fractions. These fractions were monitored by tlc. Fraction 1 (365 mg, mp 89–97°) was primarily N-carbobenzoxy-S-benzyl-cysteine thiobenzyl ester contaminated with some starting material and *p*-nitrophenol. Fractions 2

(16) Previously reported mp 171–173° and $[\alpha]^{21}D$ −34.3 (*c* 0.7, chloroform): J. Kovacs, M. Q. Ceprini, C. A. Dupraz, and G. N. Schmit, *J. Org. Chem.*, **32**, 3696 (1967).

TABLE IV

REACTION OF CARBOBENZOXY-S-BENZYL-L-CYSTEINE ACTIVE ESTERS WITH BENZYL MERCAPTAN IN THE PRESENCE OF TRIETHYLAMINE

Starting Ester X of Z-Cys-X (BZL)	Product X of Z-Cys-X (BZL)	Yield, %	Mp, °C	Registry no.
OSu	SBZL[a]	80[b]	75–77	
ONP	SBZL[a]	83[b]	73–76	
OPFP	SBZL[a]	83[b]	74–76	
ODNP (2,4)	SBZL[a]	86[b]	75–76	
OTCP[c] (2,4,5)	SBZL[a]	82[b]	72–76	
OTCP[c] (2,4,6)	OTCP[e] (2,4,6)	90[d]	107–109	5276-82-4
OTBP[c] (2,4,6)	OTBP[e] (2,4,6)	92[d]	110–112 (softening above 98°)	24164-39-4
OPBP[c]	OPBP[e]	87[d]	192–193	24164-49-6
OPCP	OPCP	87	168–169	

[a] Products were identified by comparison of the ir spectrum in chloroform with those of the optically pure L isomers and also by tlc. [b] Once crystallized from ether–hexane. [c] Tetrahydrofuran as reaction solvent. [d] Crude solid washed with *n*-hexane. [e] Characterized by elemental analysis and ir spectrum.

and 3 (679 mg) showed only the thiobenzyl ester on tlc. Fractions 4 and 5 were mainly *p*-nitrophenol and were discarded. Fractions 2 and 3 were combined and recrystallized from absolute methanol. The yield was 205 mg, mp 77–78°, $[\alpha]^{22}D$ −25.4° (c 1, dimethylformamide). This sample of thiobenzyl ester exhibited 3139 ± 25 cpm/μmol. The sample gave an identical infrared spectrum in chloroform solution with that of an authentic sample of N-carbobenzoxy-S-benzyl-L-cysteine thiobenzyl ester.

Anal. Calcd for $C_{25}H_{25}NO_3S_2$: C, 66.49; H, 5.58; N, 3.10; S, 14.20. Found: C, 66.30; H, 5.96; N, 3.36; S, 13.94.

A portion of the recrystallized thiobenzyl ester (167 mg, 0.37 mmol) was dissolved in 1 ml of absolute ethanol. Hydrazine, 95% (0.06 ml), was added and the reaction mixture was allowed to stand overnight. The reaction mixture was diluted with 20 ml of ether and then pentane to precipitate the hydrazide. The hydrazide was filtered and washed with pentane. The yield was 132 mg (99%). The hydrazide was recrystallized from ether–pentane containing 1 ml of methanol. The white crystalline solid was filtered, mp 120–121°. The identity of this compound was established by comparison of its ir spectrum in chloroform solution with that of an authentic sample of N-carbobenzoxy-S-benzyl-L-cysteine hydrazide. The hydrazide (10 mg) was dissolved in 24 ml of scintillation grade toluene and 1 ml of absolute methanol. This sample of hydrazide showed 4 ± 0.6 cpm/μmol.

Reaction of N-Carbobenzoxydehydroalanine Pentachlorophenyl Ester with Benzyl Mercaptan.—N-Carbobenzoxydehydroalanine pentachlorophenyl ester (469 mg, 1 mmol) was dissolved in 20 ml of chloroform. Benzyl mercaptan (124 mg, 1 mmol) and triethylamine (1 ml, 7.1 mmol) were added to the solution and the mixture was stirred at room temperature for 105 min. The solvent and triethylamine were removed *in vacuo* at room temperature. The solid residue was triturated with pentane, filtered, and washed with pentane. N-Carbobenzoxy-S-benzyl-DL-cysteine pentachlorophenyl ester was isolated in 79% yield, mp 164–165°.

Anal. Calcd for $C_{24}H_{18}NO_4SCl_5$: C, 48.55; H, 3.06; N, 2.36. Found: C, 48.75; H, 3.43; N, 2.42.

Ester Exchange Reaction of N-Carbobenzoxy-S-benzyl-L-cysteine Active Ester with Benzyl Mercaptan in the Presence of Triethylamine.—A typical example is given below. To a solution of 0.221 g (0.5 mmol) of N-carbobenzoxy-S-benzyl-L-cysteine N-hydroxysuccinimide ester in dry chloroform (10 ml) at room temperature, 0.06 ml (0.5 mmol) of benzyl mercaptan and 0.5 ml (3.6 mmol) of dry triethylamine were added. After 3 hr the reaction mixture was cooled and diluted with 10 ml of chloroform. The organic phase was washed with 1 *N* hydrochloric acid and water and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The colorless thick oil solidified on trituration with ether–hexane. It was recrystallized from the same solvent affording 191 mg (80%) of the thiobenzyl ester, mp 75–77°. Identity of this compound was proved by comparison of its ir spectrum in chloroform solution with that of an authentic sample and also by tlc. See Table IV.

Racemization Rate Studies on Active Esters.—All operations needed for preparation of the solutions for these rate studies were carried out in a glove bag under a dry nitrogen or helium atmosphere. The concentration of the active esters in tetrahydrofuran was between 0.314 and 0.514 *M*. The racemization was initiated by adding 7 equiv of triethylamine to this solution. All kinetics were followed at 589 mμ. The first reading was taken within 2 min of mixing the reagents. The pseudo-first-order plots were linear up to 90% racemization for all the esters except for the 2,4-dinitrophenyl ester which was linear up to 60–70% racemization. The second-order rate constants listed in Table I were obtained by dividing the pseudo-first-order rate constants by the triethylamine concentration. The racemization rate studies with 1 and 35 equivalents of triethylamine were run in a similar manner, but the data are not reported.

Aminolysis Rate Studies on Active Esters.—A tetrahydrofuran solution which was 0.13 *M* in N-carbobenzoxy-S-benzyl-L-cysteine active ester and 0.13 *M* in valine methyl ester was used to study the aminolysis of all esters except the pentachlorophenyl ester where 0.0845 *M* solutions were used.

The courses of the reactions were followed using a double-beam infrared spectrometer by monitoring the disappearance of the active ester carbonyl band in the 5.6-μ region. A sealed 0.1-mm NaCl cell was used for the sample solutions; a matched NaCl cell containing the solvents was in the reference beam. Conformance to Beer's law was checked for all esters studied throughout the pertinent concentration ranges.

For the slower reactions, the spectrum between 5 and 6 μ was scanned periodically throughout the reaction. Net absorbances were estimated using the base-line method. At least 10 data points were taken for each run.

For the faster reactions, the spectrometer was set on the absorbance maximum of the active ester carbonyl peak and the pen excursion at this wavelength was monitored as a function of time. In all such cases, the initial reading was taken within 20 sec of mixing. Using this technique, a minimum of ten data points was obtained for each run. With this technique rate constants up to 1.0 M^{-1} sec^{-1} can be easily estimated.

Coupling of N-Carbobenzoxy-S-benzyl-L-cysteinyl Pentafluorophenyl Ester with Valine Methyl Ester.—N-Carbobenzoxy-S-benzyl-L-cysteine pentafluorophenyl ester (1.5 g, 2.9 mmol) was added to 402 mg (3.1 mmol) of valine methyl ester dissolved in 22.8 ml of tetrahydrofuran and the solution was stirred for 5 min at room temperature and worked up in the usual manner, yield 90%. The residue was triturated with pentane and the solid was filtered and washed thoroughly with pentane, yield 1.06 g (80%), mp 78–79°. Recrystallization from ethyl acetate pentane raised the melting point to 79–80°, $[\alpha]^{22}D$ −30.1° (c 2, tetrahydrofuran).

Anal. Calcd for $C_{24}H_{30}N_2O_5S$: C, 62.86; H, 6.59. Found: C, 62.85; H, 6.47.

Racemization Study of N-Carbobenzoxy-S-benzyl-L-cysteine *p*-Nitrophenyl Ester during Coupling.—A solution of the *p*-nitrophenyl ester (2.98 g, 6.4 mmol) and 1.7 ml (12.8 mmol) of valine methyl ester in 50.0 ml of tetrahydrofuran was allowed to react for 200 hr. The rotation of the solution after 200 hr was α 1.274. The following solution was prepared as a control: 0.117 g (0.256 mmol) of the aforementioned dipeptide, 0.0356 g (0.256 mmol) of *p*-nitrophenol, and 0.0329 g (0.256 mmol) of

valine methyl ester dissolved in 2.0 ml of tetrahydrofuran. The value of this solution was −1.259 indicating there was not any significant racemization.

N-Carbobenzoxy-S-benzyl-L-Cysteinylglycine p-Nitrophenyl Ester.—Glycine *p*-nitrophenyl ester hydrobromide (0.277 g, 0.001 mmol) was dissolved in dimethylformamide (2 ml) and tetrahydrofuran (20 ml) was added, followed by the addition of N-carbobenzoxy-S-benzyl-L-cysteine pentafluorophenyl ester (0.511 g, 0.001 mmol). The solution was cooled to −10°, and triethylamine (0.14 ml, 0.001 mol) was added. After 10 min at −10° and 20 min at room temperature, the mixture was filtered. Ethyl acetate (25 ml) was added to the filtrate, and the solution washed with saturated sodium chloride. The dried solution was evaporated and the residue triturated with ether. Filtration gave 0.364 g (70%) of a crude product, mp 150–153°. This material was dissolved in 20 ml of hot methanol and tetrahydrofuran mixture (1:1) and diluted with an equal volume of ether. On cooling a small amount of white solid separated which was discarded. The filtrate on dilution with an excess of hexane afforded the desired dipeptide, 0.260 g, mp 158–159°, $[\alpha]^{22}D$ −26.85 (c 2, tetrahydrofuran).

Anal. Calcd for $C_{26}H_{25}N_3SO_7$: C, 59.65; H, 4.81; N, 8.02. Found: C, 59.30; H, 4.88; N, 8.29.

Registry No.—N-Carbobenzoxydihydroalanine pentachlorophenyl ester, 24164-70-3; N-carbobenzoxydehydroalanine *p*-nitrophenyl ester, 24164-71-4; N-carbobenzoxy-S-benzyl-L-cysteine pentabromophenyl ester, 24164-49-6; N-carbobenzoxy-S-benzyl-2,4,6-tribromophenyl ester, 24164-39-4; N-carbobenzo-S-benzyl-2,4,5-trichlorophenyl ester, 24164-40-7; N-carbobenzoxy-S-benzyl-2,4-dinitrophenyl ester, 23180-03-2; N-carbobenzoxy-S-benzyl-2,6-dinitrophenyl ester, 24164-42-9; N-carbobenzoxy-S-benzylthiobenzyl ester, 24164-43-0; (±)-N-carbobenzoxy-S-benzylcysteinepentachlorophenyl ester, 24164-44-1; (±)-N-carbobenzoxy-S-benzylcysteine thiobenzyl ester, 24164-45-2; N-carbobenzoxy-S-benzylcysteine thiobenzyl ester hydrazide, 24164-46-3; N-carbobenzoxy-S-benzyl-L-cysteinyl pentafluorophenyl ester valine methyl ester dipeptide, 24215-87-0; N-carbobenzoxy-S-benzyl-L-cysteinylglycine *p*-nitrophenyl ester, 7669-99-0.

Acknowledgment.—This work was supported by grants from the National Institutes of Health (GM No. 06579 and 08795). We wish to thank Professor H. Horan for the infrared spectra.

The Rotational Barrier in 1,8-Diarylnaphthalenes[1a]

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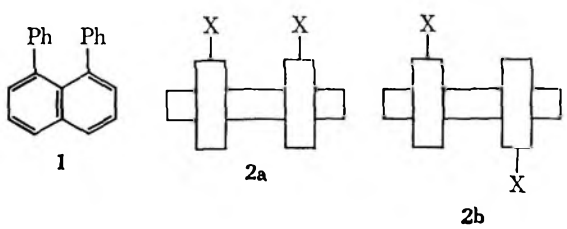
A series of 1-phenyl-8-(3-substituted phenyl)naphthalenes, **5**–**8**, have been synthesized to examine the question of the ease of rotation of the aryl rings in 1,8-diarylnaphthalenes. Although a number of 1,8-diphenylnaphthalenes with substituents in the phenyl rings exhibit temperature-dependent nmr spectra, the spectra are normally too complex for simple interpretation. However, the nonequivalence of the methyl signals in the low-temperature nmr spectrum of the derivative **8a** with a *meta* 2-hydroxy-2-propyl substituent provides unambiguous evidence for the rotation of the substituted phenyl ring in this substance. The free energy of activation ($\Delta G^{\ddagger}$) for this rotation is calculated to be 16 kcal/mol at 25°.

Various evidence[2,3] indicates the favored conformation of 1,8-diphenylnaphthalene (**1**) to be one in which the two phenyl rings are parallel to one another and perpendicular to the plane of the naphthalene ring as illustrated by a top view of the molecule in structure **2**. Consideration of the dimensions of such molecules as discerned from molecular models and the limited X-ray crystallographic data available[2] suggests the existence of a substantial energy barrier to rotation of the phenyl rings and led us to expect that *cis* (**2a**) and *trans* (**2b**)



1 **2a** **2b**

isomers of 1,8-di(*ortho*- or *meta*-substituted phenyl)-naphthalenes might be isolated. In fact, we were completely unsuccessful in this attempt and instead isolated a series of di-*meta*-substituted compounds as single crystalline substances.[3] Nmr and dipole moment data obtained from certain of these compounds suggested that equilibration of the two geometrical isomers **2a** ⇌ **2b** may be relatively rapid in solution with an energy barrier to rotation on the order of 10 kcal/mol. Since this energy barrier seemed unusually low and the interpretation of our data for these disubstituted compounds (**2**) was not unambiguous, we have sought more convincing evidence about this rotation barrier. This paper describes the preparation of a series of monosubstituted diphenylnaphthalenes (Scheme I) and appropriate nmr measurements which clearly demonstrate the rotation of the substituted phenyl ring in solution at 25°.

The synthetic route (Scheme I) followed our earlier pattern[3] in which the unsaturated ketone **3** was converted to a diene **4** which was dehydrogenated to the diarylnaphthalene **5**. This aryl chloride **5** was converted to the cyanide **6** with CuCN in HMP[4] and then hydrolyzed to the acid **7a**. This acid **7a** (pK^*_{MCS} = 7.04)[5] is slightly less acidic than the corresponding monoarylnaphthalene derivative **9a** (pK^*_{MCS} = 6.50–6.56)[3,5] possibly reflecting the increased steric hindrance to solvation of the carboxylate anion from acid **7a**.

(1) (a) This research has been supported by Public Health Service Grant 1-R01-CA10933 from the National Cancer Institute; (b) National Institutes of Health Predoctoral Fellow, 1968–1970.

(2) For a review, see V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(3) (a) H. O. House and R. W. Bashe, II, *J. Org. Chem.*, **30**, 2942 (1965); **32**, 784 (1967). (b) H. O. House, R. W. Magin, and H. W. Thompson, *ibid.*, **28**, 2403 (1963), and references therein.

(4) H. O. House and W. F. Fischer, Jr., *ibid.*, **34**, 3626 (1969).

(5) The values pK^*_{MCS} are the apparent pK_a values in a mixture of 20% water and 80% Methyl Cellosolve: W. Simon, *Angew. Chem., Int. Ed. Engl.*, **3**, 661 (1964).

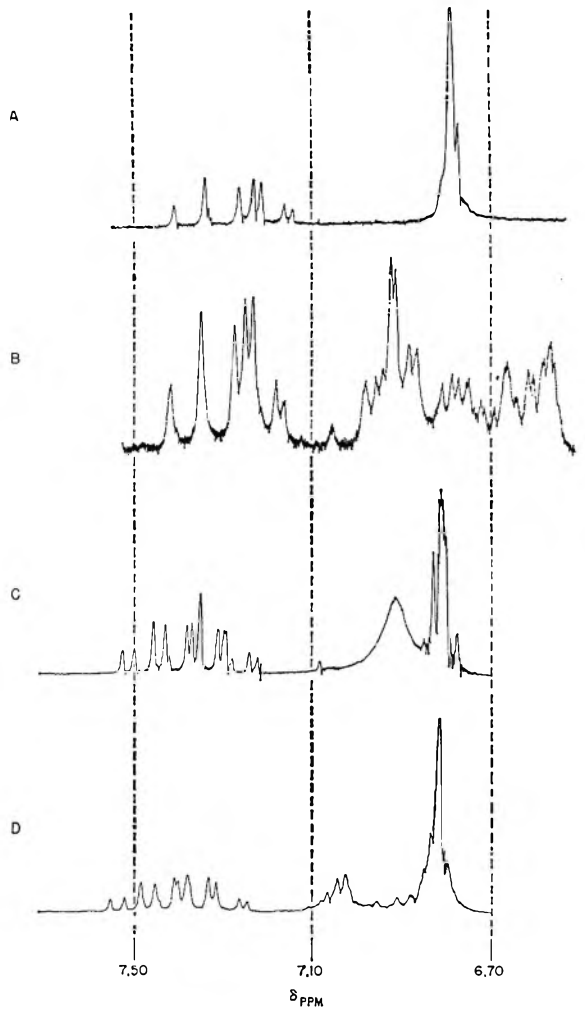
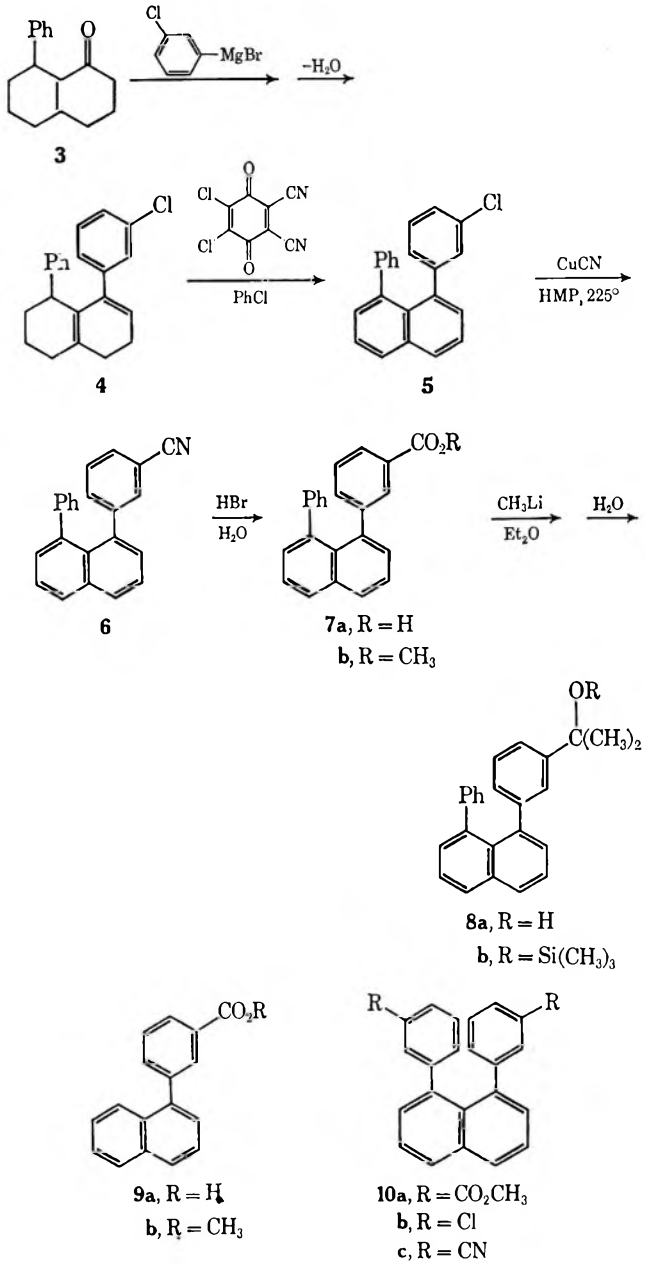


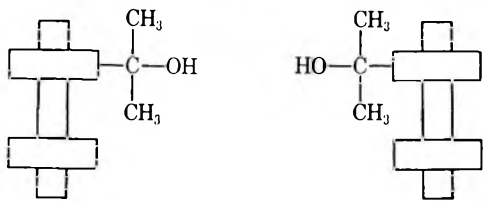
Figure 1.—Nmr spectra (100 MHz) of the aryl and high-field (4 H) naphthyl regions for (A) the dichloro derivative **10b** in $Cl_2C{=}CCl_2$ at 119°; (B) the dichloro derivative **10b** in $Cl_2C{=}CCl_2$ at −25°; (C) the monochloro derivative **5** in $CDCl_3$ at 50°; (D) the monochloro derivative **5** in $CDCl_3$ at −7°.

In earlier work[3] the nmr O–Me singlet for the diester **10a** was observed to broaden and then split into a closely spaced doublet as solutions of the diester were cooled below 20°. Further indications of conformational changes have now been found in the comparison of room temperature and lower temperature nmr spectra of the aryl derivatives **1**, **5**, **7b**, and **10b**. Figure 1 illustrates several of these spectra at relatively low and high temperatures for the monochloro and dichloro derivatives **5** and **10b**. Although the lower field region (δ 7.0–7.5, the four higher field naphthyl CH) of the spectra undergo only minor variations, the patterns observed in the higher field region (δ 6.5–7.0, phenyl or *m*-chlorophenyl CH) are strikingly dependent on temperature. Similar, although less pronounced, changes are seen for the absorption of phenyl protons in the 100-MHz spectrum of 1,8-diphenylnaphthalene in the temperature range +56 to −18.5°. The nmr spectrum of the monoester **7b** exhibited only a single methoxyl peak throughout the temperature range from −5 to +65°. This observation suggests that the doublet for the methoxy groups observed in the nmr spectrum of the diester **10c** at temperatures below 10° is probably attributable to conformations **2a** and **2b** and not to conformations involving rotation of the carbomethoxy groups with respect to the phenyl ring.

SCHEME I

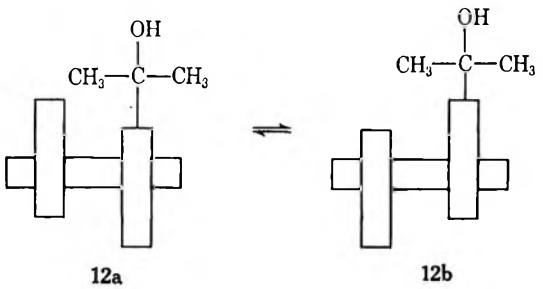


Although these variations in nmr pattern with temperature were indicative of the slowing down of some sort of conformational change, the complexity of the absorption patterns in 60- and 100-MHz spectra made a detailed interpretation difficult. For this reason the dimethylcarbinol **8a** was synthesized with the expectation that two different nmr C–Me signals would be seen if the grouping $Me_2C(OH)$– was bound to an asymmetric environment such as the *meta* position of a nonrotating phenyl ring in 1,8-diphenylnaphthalene as in structure **11a**. If the ring to which the group was bonded were able to rotate rapidly, the resulting racemization process **11a** ⇌ **11b** would average the



11a **11b**

positions of two nmr C–Me signals to give a single line. As illustrated in Figure 2, precisely this behavior is observed in spectra measured at various temperatures. This observation requires rotation of the substituted phenyl ring and is not compatible with other conformational changes such as the distorted conformations illustrated in structures **12** which would not racemize the molecule.



12a **12b**

The observed variation in C–Me signals with temperature (Figure 2, B, C, and D) was simulated (Figure 2, E, F, and G) with a computer program[6] to allow determination of the pre-exchange lifetimes, τ, at various temperatures. From these the activation energy, $\Delta G^{\ddagger}$, for rotation of the *substituted* phenyl ring in the carbinol **8a** was calculated to be 16 kcal/mol at 25°. With a rotation barrier this low our failure to isolate the *cis* and *trans* isomers **2a** and **2b** in our earlier study[3a] becomes understandable.

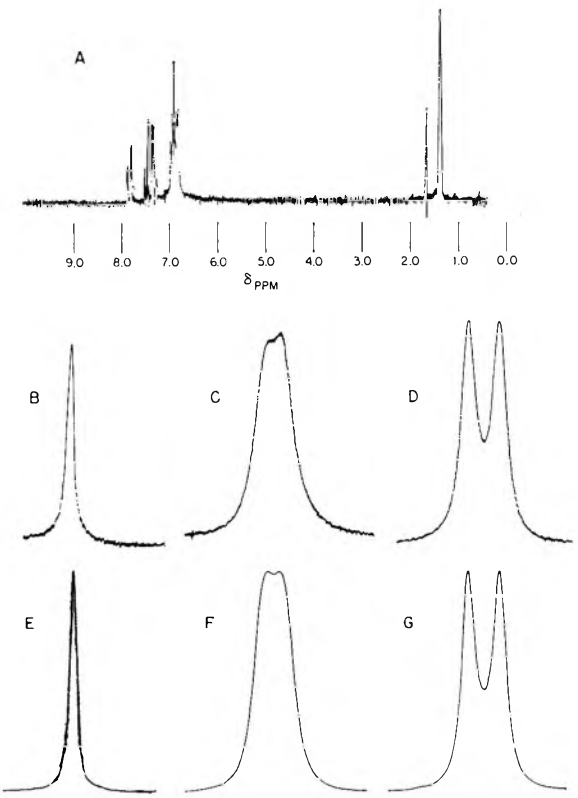


Figure 2.—Nmr spectra (100 MHz, sweep widths of 1000 Hz for A and 50 Hz for B–G) of the dimethylcarbonol **8a** in $CDCl_3$: (A) complete spectrum at 27°, (B) observed C-methyl peak at 65.2°; (C) observed C-methyl peak at 27.6°; (D) observed C-methyl peaks at 10.0°; curves E, F, and G are computer simulated spectra corresponding to observed spectra B, C, and D with τ values of 0.006, 0.155, and 0.500 sec. The peak separation in the slow exchange limit is 3.5 Hz.

Experimental Section[7]

Preparation of the Diene 4.—A solution of 155 mmol of *m*-chlorophenylmagnesium bromide[3a] in 234 ml of Et_2O was treated with a solution of 28.37 g (127 mmol) of the previously described[3a,8] conjugated ketone **3** (mp 74.2–75.3°) in 100 ml of Et_2O. After the resulting mixture had been stirred at 25° for 21 hr, aqueous NH_4Cl was added. The combined Et_2O layer and the Et_2O extract of the aqueous phase were washed with aqueous $NaHCO_3$, dried, and concentrated to leave 33.19 g of the crude alcohol intermediate as a yellow liquid: ir (CCl_4) 3575 cm^{-1} (OH); nmr (CCl_4) δ 6.7–7.2 (9 H, m, aryl CH), 3.0–3.2 (1 H, m, benzylic CH), and 1.4–2.4 (12 H, m, aliphatic CH). A solution of the crude alcohol in 400 ml of Ac_2O was refluxed for 24 hr and then concentrated under reduced pressure. After a solution of the residual liquid in Et_2O had been washed with aqueous $NaHCO_3$, dried, and concentrated, the crude diene **4** remained as 29.39 g of yellow liquid. Chromatography (silica gel) separated 11.50 g of the diene as a colorless liquid fraction (eluted with 4:1 v/v hexane–benzene) which was crystallized from hexane to separate 7.57 g (18.6%) of the pure diene **4** as colorless prisms: mp 81–82°; ir (CCl_4) no OH or C=O in the 3- or 6-μ regions; uv (95% EtOH) 261 mμ (br, ϵ 12,400);[9] nmr (CCl_4) δ 6.2–7.4 (9 H, m, aryl CH), 5.4 (1 H, m, vinyl CH), 3.45 (1 H, m, benzylic CH), and 1.3–2.5 (10 H, m, aliphatic CH); mass spectrum, *m/e* (relative intensity), 322 (8), 321 (36), 320 (25), 319 (100), 216 (27), 167 (24), 141 (36), 99 (50), 91 (29), 57 (72), 56 (58), 43 (55), 42 (34), and 41 (61).

Anal. Calcd for $C_{22}H_{21}Cl$: C, 82.35; H, 6.60; Cl, 11.05. Found: C, 82.08; H, 6.67; Cl, 11.35.

Preparation of the *m*-Chloro Derivative 5.—A solution of 1.00 g (3.12 mmol) of the diene **4** and 2.20 g (9.7 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone in 45 ml of PhCl was refluxed for 22 hr under N_2 and then was concentrated under reduced pressure. After the residue had been extracted with three portions of boiling hexane, the combined hexane solutions were filtered through 50 g of alumina (activity grade II) and then concentrated, to leave 1.10 g of the crude chloride **5** as a colorless liquid. The product **5** crystallized from hexane as 397 mg (40%) of white needles, mp 88.6–89.9°. Sublimation (112° and 0.1 mm) afforded the pure chloride **5**: mp 89–90°; ir (CCl_4) no OH or C=O in the 3- or 6-μ regions; uv (95% EtOH) 235 mμ (ϵ 49,400), and 300 (11,800);[10] nmr (CCl_4) δ 6.8–8.1 (m, aryl CH) (for variations with temperature, see Figure 1); mass spectrum, *m/e* (relative intensity) 316 (21), 314 (60), 132 (33), 104 (31), 103 (29), 44 (100), and 43 (56).

Anal. Calcd for $C_{22}H_{15}Cl$: C, 83.93; H, 4.80; Cl, 11.26. Found: C, 83.77; H, 4.97; Cl, 11.39.

Preparation of the Nitrile 6.—A solution of 5.19 g (16.5 mmol) of the chloride **5** and 14.8 g (165 mmol) of CuCN in 21 ml of hexamethylphosphoramide was heated to 225° under an N_2 atmosphere for 2.5 hr and then cooled and poured into aqueous NaCN. The benzene extract of the mixture was washed successively with H_2O, aqueous HCl, aqueous $NaHCO_3$, H_2O, and aqueous NaCl, and then dried and concentrated. The residual yellow solid (5.52 g) was fractionally crystallized from hexane to separate 4.35 g (86%) of fractions of the crude nitrile **6** melting within the range 89.5–112.5°.

Recrystallization of the crude nitrile **6** from hexane afforded samples melting within the range 112–115° which contained

(6) J. B. Lisle, B. S. Thesis, Massachusetts Institute of Technology, June 1968.

(7) 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 recording spectrophotometer, Model 14. The nmr spectra were determined with a Varian Model A-60, T-60, or HA-100 nmr spectrometer. The chemical-shift values are expressed either in Hz or δ values (ppm) relative to a tetramethylsilane or hexamethyldisiloxane internal standard. The mass spectra were obtained with Hitachi (Perkin-Elmer) mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

(8) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 360 (1963).

(9) The analogous di-*m*-chlorophenyl diene[3a] has an ultraviolet maximum at 258 mμ (ϵ 11,100). As noted elsewhere,[3a] we believe these uv data are more consistent with a 2-aryl-1,3-butadiene chromophore rather than a 1-aryl-1,3-butadiene derivative.

(10) The corresponding uv data for the other 1,8-diarylnaphthalenes are 235.5 mμ (ϵ 54,500) and 300 (11,500) for **1**,[3b] and 234 mμ (ϵ 58,400) and 300 (21,500) for **10b**.[3a]

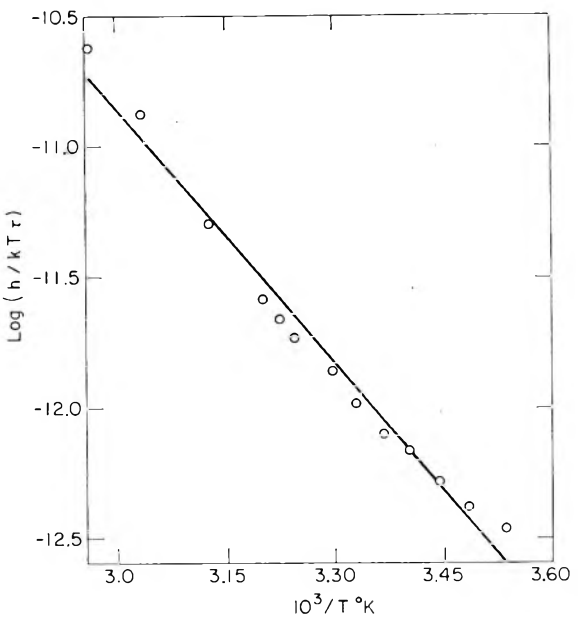


Figure 3.—Plot of log $(h/kT\tau)$ as a function of $1/T$ for the dimethylcarbinol **8a** in $CDCl_3$. The slope of this line is $-\Delta H^{\pm}/2.303R$.

(glpc analysis, silicone gum SE-52) the nitrile **6** (retention time *ca.* 25 min) accompanied by *ca.* 3% of the starting chloride **5** (retention time 12.8 min). A collected (glpc) sample of the nitrile was recrystallized from hexane to separate the pure nitrile **6** as white prisms, mp 127.5–128.5°. After sublimation (140° and 0.1 mm), the nitrile melted at 128–129°: ir ($CHCl_3$) 2225 cm^{-1} (C≡N); uv max (95% EtOH) 229 mμ (ε 47,900) and 301 (10,600); nmr ($CDCl_3$) δ 7.3–8.2 (6 H, m, naphthyl CH) and 6.7–7.3 (9 H, m, phenyl CH); mass spectrum, *m/e* (relative intensity) 306 (25), 305 (100, M^+), 304 (18), 203 (11), 202 (9), 149 (9), and 138 (8).

Anal. Calcd for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.56; H, 4.85; N, 4.24.

Preparation of the Acid Derivative 7.—A mixture of 5.36 g (16.6 mmol) of the nitrile **6** and 50 ml of aqueous 48% HBr was refluxed for 16 hr and then concentrated under reduced pressure. A solution of the residue in Et_2O was extracted with aqueous Na_2CO_3, and the combined aqueous solutions were acidified (HCl) and extracted with Et_2O. The latter Et_2O solution was dried and concentrated to leave 2.13 g of crude acid as a yellow solid. The neutral material (2.89 g) from this hydrolysis was refluxed with a mixture of 30 ml of aqueous 48% HBr and 50 ml of HOAc for an additional 48 hr and then subjected to the same work-up procedure to separate 0.95 g of crude acid. The combined acidic products were recrystallized from a hexane–EtOAc mixture to separate 2.14 g (38%) of the acid **7a** as a pale yellow solid, mp 224.6–226°. Further purification involving partitioning between Et_2O and aqueous Na_2CO_3, acidification, and recrystallization gave the pure acid as white prisms: mp 225–226.5°; ir (KBr pellet) 1685 cm^{-1} (br, carboxyl C=O); uv (95% EtOH) 232 mμ (ε 53,800) and 301 (11,800); nmr [$(CD_3)_2SO$] δ 6.8–8.4 (m, aryl CH).

Anal. Calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 84.93; H, 5.07.

The pK^*_{MCS} value[5] for the acid **7a** at 25° was 7.04 compared with a value of 6.56[3a] for the acid **9a**. A 1.25-g (3.85 mmol) sample of the acid **7a** was esterified with excess ethereal CH_2N_2. The crude neutral product, 1.245 g of yellow oil, was crystallized from MeOH to give 1.04 g (81%) of the ester **7b** as white prisms: mp 84.5–85.7° (recrystallization raised the melting point to 86.1–87.1°); ir (CCl_4) 1725 cm^{-1} (conjugated ester C=O); uv (95% EtOH) 231 mμ (ε 52,000) and 300 (11,200); nmr ($CDCl_3$) δ 6.7-8.0 (15 H, m, aryl CH) and 3.75 (3 H, s, OCH_3); mass spectrum, *m/e* (relative intensity) 338 (100), 279 (18), 252 (19), 138 (25), and 126 (18).

Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 84.97; H, 5.47.

Preparation of the Dimethylcarbinol 8a.—A solution of 502 mg (1.48 mmol) of the ester **7b** in 15 ml of Et_2O was added to 25 ml of an ethereal solution containing 3.97 mmol of MeLi. The mixture was stirred at 25–30° for 45 min and then mixed with aqueous NH_4Cl. The Et_2O layer and the Et_2O extract of the aqueous phase were combined, washed with aqueous $NaHCO_3$, dried, and concentrated. After considerable effort the residual oil (501 mg) was successfully crystallized from hexane at Dry Ice temperatures to separate 265 mg (53%) of the carbinol **8a** as white needles: mp 97.6–98.6°; ir (CCl_4) 3560 and 3590 cm^{-1} (OH); uv max (95% EtOH) 236 mμ (ε 51,700) and 301 (11,300); nmr ($CDCl_3$) δ 6.7–8.1 (15 H, aryl CH), 1.62 (1 H, s, OH), and 1.40 (6 H, s, CCH_3).

Anal. Calcd for $C_{25}H_{22}O$: C, 88.72; H, 6.55. Found: C, 89.03; H, 6.50.

In an effort to increase the separation of peaks (see Figure 2, solutions in $CDCl_3$) for the methyl signals of the carbinol **8a**, the spectrum was examined in other solvents. A comparable peak separation was observed in PhCl, and the addition of pyridine to the solution resulted in a collapse of the doublet to a broad single line. A broad single line was also observed in CD_3COCD_3. A solution of 2.18 mmol of MeLi in 1.0 ml of 1,2-dimethoxyethane (DME) was treated with 245 mg (0.728 mmol) of the ester **7b**. The resulting solution of the lithium salt of the carbinol **8a** was treated with a solution of 1.31 ml (10.0 mmol) of Me_3SiCl and 0.5 ml of Et_3N in 3.0 ml of DME which had been centrifuged to remove any Et_3NHCl. The mixture was stirred at 25° for 1 week and then partitioned between aqueous $NaHCO_3$ and pentane. The pentane solution was dried and concentrated to leave 260 mg of yellow liquid which contained (tlc on silica gel with $CHCl_3$ eluent) the silyl ether **8b** (most rapidly eluted) and a second unknown component eluted more rapidly than the alcohol **8a**. One-fourth of this material was chromatographed on silica gel to separate 51 mg of fractions [eluted with a hexane–benzene mixture (4:1 v/v)] containing the crude silyl ether **8b** as a colorless liquid: ir (CCl_4) no OH or C=O in the 3- or 6-μ regions; uv (95% EtOH) 235 mμ (ε 46,700) and 302 (10,500); nmr ($CDCl_3$) δ 6.9–7.7 (6 H, m, naphthyl CH), 6.4–6.9 (9 H, phenyl CH), 1.43 (6 H, s, CH_3C), and 0.08 (9 H, s, CH_3Si). Even at a low temperature (−20°), only a single nmr peak was seen for the two C-methyl groups. The mass spectrum exhibited the following abundant peaks: *m/e* (relative intensity) 410 (M^+, 40), 396 (35), 395 (100), 75 (19), and 73 (43).

Calculation of the Rotational Barrier.—The exchange-broadened nmr spectra were calculated and plotted with the aid of the computer program EXCNMR[6] employing the usual density matrix formalism.[11] In this study, the *measured* line width at half-height was 0.8 Hz at the high-temperature limit (65°). Based on measured values in observed spectra, the line width was assumed to vary from 0.7 to 1.0 Hz in going from 63 to 10°. The relative populations are, of course, equal, and a coupling constant, $J = 0$, was assumed between the protons on the two methyl groups. Below the coalescence temperature the line separation increased to 3.5 Hz (at 10°); this separation remained constant as the temperature was decreased to −5.6°. Below this temperature broadening of the lines became a sufficiently serious problem so that meaningful values for the peak separations could not be obtained.

Calculated and observed spectra were compared by matching line widths above coalescence and by matching peak separation and depth of "valley" as well as line widths at lower temperatures. The Arrehenius activation parameters (E_A and A) and the transition-state parameters ($\Delta S^{\pm}$, $\Delta H^{\pm}$, $\Delta G^{\pm}$) were calculated from the set of observed temperatures and their corresponding pre-exchange lifetimes, τ, using standard techniques.[12] In these calculations the per cent error in the values of τ was assumed to be ±5%, and the standard deviation in measuring the temperature was taken as ±0.5°. A least-squares calculation was made fitting the functions

$$F = \ln(h/kT\tau) - \Delta S^{\pm}/R + (\Delta H^{\pm}/R)(1/T)$$

where k is the Bolzmann constant, h is Planck's constant, $\Delta S^{\pm}$ is the entropy of activation, and $\Delta H^{\pm}$ is the enthalpy of activation.[13]

(11) (a) S. Alexander, *J. Chem. Phys.*, **37**, 967, 974 (1962); **38**, 1787 (1963); **40**, 2741 (1964). (b) C. S. Johnson, Jr., *Advan. Magn. Resonance*, **1**, 33 (1965).

(12) G. Binsch, *Top. Stereochem.*, **3**, 97 (1968).

(13) These calculations were carried out using a modification of the program ACTENG, written by D. F. DeTar, and obtained from the Quantum Chemistry Program Exchange, Bloomington, Ind.

The free energy of activation, $\Delta G^{\pm}$, was then calculated from the $\Delta H^{\pm}$ and $\Delta S^{\pm}$ values at 25° with the usual relationship, $\Delta G^{\pm} = \Delta H^{\pm} - T\Delta S^{\pm}$. The data and calculated values were printed, and a plot was drawn (Figure 3) of log $(H/kT\tau)$ *vs.* $1/T$ where T is in degrees Kelvin. The values calculated from a series of measurements including those illustrated in Figure 2 were $\Delta G^{\pm} = 16.4 \pm 0.2$ kcal/mol; $\Delta H^{\pm} = 14.8 \pm 0.2$ kcal/mol; $\Delta S^{\pm} = -5.4 \pm 0.5$ eu. Because of the relatively small separation of lines (3.5 Hz in the low-temperature limit) and the tendency of the lines to broaden at lower temperatures, we believe more realistic probable limits of error for $\Delta G^{\pm}$ and $\Delta H^{\pm}$ are ±2 kcal/mol with a reasonable probability for substantial error in the value of $\Delta S^{\pm}$.

Registry No.—**4**, 24299-67-0; **5**, 24299-68-1; **6**, 24299-69-2; **7a**, 24299-70-5; **7b**, 24299-71-6; **8a**, 24299-72-7; **8b**, 24299-73-8; **10b**, 7731-47-7.

Relationships between Structure, Polarography, and Electronic Spectra of 4- and 5-Substituted 2-Nitrophenols[1a]

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Polarographic oxidation potential, $E_{1/2}$(OX), and reduction potentials, $E_{1/2}$(RED), for a series of 4- and 5-substituted 2-nitrophenols have been measured in aqueous ethanol (10%) solutions buffered at pH 2.2, 4.0, 6.0, 8.0, and 9.2. Although both series appear to give polarographic waves characteristic of irreversible reactions, good correlations of $E_{1/2}$(OX) and $E_{1/2}$(RED) with the appropriate substituent constant, σ_m, σ_p, or $\sigma_p^{\pm}$, were obtained. Usually, the correlations that involved $E_{1/2}$(RED) were most satisfactory at low pH, while those that involved $E_{1/2}$(OX) were best at high pH. The correlation of the frequency of the longest wavelength maximum observed in the electronic spectrum with $E_{1/2}$(OX) or $[E_{1/2}(\text{OX}) - E_{1/2}(\text{RED})]$ was examined and found to be good for the 4-substituted compounds and poor for the 5-substituted ones. For the most widely divergent data, an attempt to explain the discrepancies has been made, but the investigation of other series would be desirable.

On the basis of a naive molecular orbital theory, a number of physical properties have been related to the positions of calculated energy levels of organic molecules.[2] In particular, polarographic oxidation and reduction potentials have been correlated with the calculated energy levels of the ground and first excited states, respectively,[2a] and the frequencies of certain spectral transitions have been correlated with the differences in energy between these levels.[2b]

Rather than depending upon the accuracy of such calculations for the correlation of physical and chemical properties, Simpson, Hancock, and Meyers[3a] measured the electronic spectra of some 4-substituted 2-chlorophenols in acidic and basic aqueous ethanol (5%) and initiated polarographic studies of these materials. However, only oxidation potentials could be obtained in the polarographic work. Similarly, a spectral and polarographic study[3b] of 4-substituted 2-nitroanilines was attempted but only the spectra and polarographic reduction potentials could be obtained. In this study, two series of compounds, 4- and 5-substituted 2-nitrophenols, have been examined polarographically, since these materials have a known reducible group ($-NO_2$) and a known oxidizable group ($-OH$ or $-O^-$). The electronic spectra of these compounds were obtained previously.[4,5] It was hoped that a direct comparison of spectral frequencies and the difference between polarographic oxidation and reduction potentials would be possible for substituted 2-nitrophenols and that this comparison would be independent of the accuracy of any calculations of energy levels. Moreover, Hammett[6] relations have been used (with varying degrees of success in previous studies[3,7,8]) for the correlation of spectra and polarographic half-wave potentials with structure, and it was hoped to make more extensive comparisons of these correlations for two series of closely related compounds.

Results and Discussion

The Correlation of Oxidation and Reduction Half-Wave Potentials of 4-Substituted 2-Nitrophenols (I) and 5-Substituted 2-Nitrophenols (II) with Substituent Constants.—The oxidation and reduction half-wave potentials have been measured for the compounds of series I and II at pH 2.2, 4.0, 6.0, 8.0, and 9.2; the results are shown in Tables I and II. Spectral data and σ values for the substituents are shown in Table III.

For both series, calculations of the electron changes, n, from graphs of E(RED) *vs.* log $(i_d - i)/i$ did not give integral values for n, where E(RED) is the voltage at a point on a wave front, i_d is the diffusion current, and i is the current at a voltage E(RED). Despite this indication of irreversibility, it was assumed that corresponding electrochemical reactions were obtained in reduction, since each series satisfied certain requirements proposed by Zuman[9] for the validity of such an assumption. These requirements include a similarity of the wave heights observed which indicates that the same number of electrons are being transferred in the reduction of compounds in the same series, a similarity of the graphs of $E_{1/2}$(RED) *vs.* pH, a similarity in the

(1) (a) Abstracted in part from the Ph.D. Dissertation of P. Y. R., Texas A & M University, May 1968. (b) To whom inquiries should be sent.

(2) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961: (a) pp 175, 186; (b) p 217.

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(5) C. K. Hancock and A. D. H. Clague, *ibid.*, **86**, 4942 (1964).

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TABLE I

POLAROGRAPHIC OXIDATION AND REDUCTION HALF-WAVE POTENTIALS OF 4-SUBSTITUTED 2-NITROPHENOLS

Compd	4 substituent	$E_{1/2}$(RED)[a,b] at pH 2.2	4.0	6.0	8.0	9.2	$E_{1/2}$(OX)[a,c] at pH 2.2	4.0	6.0	8.0	9.2
1	OCH_3	0.178	0.272	0.412	0.540	0.723	0.722	0.599	0.461	0.342	0.316
2	CH_3	0.207	0.300	0.443	0.571	0.745	0.884	0.773	0.612	0.565	0.549
3	H	0.193	0.273	0.422	0.653	0.744	0.999	0.865	0.686	0.603	0.621
4	C_6H_5	0.178	0.303	0.390	0.518	0.633	0.817	0.685	0.541	0.473	0.471
5	Cl	0.127	0.221	0.325	0.500	0.641	0.959	0.834	0.721	0.636	0.680
6	$COOCH_3$	0.123	0.230	0.367	0.532	0.648	1.040	0.930	0.832	0.822	0.855
7	$COCH_3$	0.142	0.237	0.394	0.576	0.701	1.047	0.916	0.824	0.817	0.847
8	NO_2	0.082	0.193	0.356	0.492	0.618					

[a] Volts *vs.* saturated calomel electrode. [b] Dropping mercury indicating electrode. [c] Graphite indicating electrode.

TABLE II

POLAROGRAPHIC OXIDATION AND REDUCTION HALF-WAVE POTENTIALS OF 5-SUBSTITUTED 2-NITROPHENOLS

Compd	5 substituent	$E_{1/2}$(RED)[a,b] at pH 2.2	4.0	6.0	8.0	9.2	$E_{1/2}$(OX)[a,c] at pH 2.2	4.0	6.0	8.0	9.2
9	OCH_3	0.283	0.375	0.518	0.647	0.825	1.039	0.906	0.748	0.648	0.655
10	CH_3	0.222	0.318	0.436	0.594	0.767	0.978	0.844	0.676	0.578	0.562
11	CH_3CONH	0.239	0.318	0.447	0.585	0.717	1.010	0.876	0.702	0.611	0.592
12	H	0.193	0.237	0.422	0.653	0.744	0.999	0.865	0.686	0.603	0.621
13	Cl	0.144	0.242	0.371	0.532	0.684	1.026	0.900	0.760	0.720	0.742
14	$COOCH_3$	0.092	0.176	0.292	0.442	0.605	1.016	0.871	0.726	0.687	0.682
15	NO_2	0.042	0.125	0.246	0.355	0.445	1.085	0.948	0.861	0.865	0.885
16	CHO	0.070	0.152	0.262	0.412	0.622	1.027	0.874	0.744	0.716	0.742

[a] Volts *vs.* saturated calomel electrode. [b] Dropping mercury indicating electrode. [c] Graphite indicating electrode.

TABLE III

SUBSTITUENT CONSTANTS AND ELECTRONIC SPECTRAL DATA FOR 4- AND 5-SUBSTITUTED 2-NITROPHENOLS

Compd	Substituent	σ_m[c]	σ_p[c]	$\sigma_p^{\pm}$[d]	4 substituent[a] ν_B[e]	4 substituent[a] ν_A[f]	5 substituent[b] ν_B[e]	5 substituent[b] ν_A[f]
1	OCH_3	0.115	−0.268	−0.778	21,978	25,575	24,510	28,980
2	CH_3	−0.069	−0.170	−0.311	23,095	27,174	23,810	28,730
3	H	0.000	0.000	0.000	24,155	28,571	23,920	28,570
4	CH_3CONH	0.248	−0.015	−0.600	23,310	26,667	24,210	28,330
5	C_6H_5	0.060	−0.010	−0.179	22,727	26,455	23,700	30,580
6	Cl	0.373	0.227	0.114	23,474	27,624	24,420	29,240
7	$COOCH_3$	0.315	0.385[g]	0.636	25,000	29,326	23,470	28,090
8	$COCH_3$	0.376	0.502	0.874	25,126	29,412	22,930	27,850
9	NO_2	0.710	0.778	1.270			22,620	27,510
10	CHO	0.382	0.425[h]	1.126			22,930	27,850

[a] Reference 4. [b] Reference 5. [c] Reference 10. [d] Reference 11. [e] ν_B in $cm^{-1} = 1/\lambda_{max}^{NaOH} \times 10^7$ for the longest wavelength. [f] ν_A in $cm^{-1} = 1/\lambda_{max}^{HCl} \times 10^7$ for the longest wavelength. [g] H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **78**, 815 (1959). [h] M. Charton, *J. Org. Chem.*, **28**, 3121 (1963); A. A. Humffray, J. J. Ryan, J. P. Warren, and Y. H. Yung, *Chem. Commun.*, 610 (1965).

character of the limiting currents, and a similarity in the degree of reversibility. Only 3-hydroxy-4-nitrobenzaldehyde (the 5-CHO compound of series II) was found to give a reduction diffusion current different from the others, and it was thought best to exclude it from the regression analysis of $E_{1/2}$(RED) *vs.* σ_p[10] or $\sigma_p^{\pm}$.[11] The 2,4- and 2,5-dinitrophenols each showed two distinct reduction waves for the two nitro groups. In both cases, the first of the two waves was used for the various correlations described below.

For both series I and II, the magnitude of the potential required for reduction increases with increasing pH (Tables I and II). The plots of reduction half-wave potentials *vs.* substituent constants (Figures 1–3) have positive slopes indicating that substituents which increase the electron density increase the magnitude of the potential required for reduction. This is to be expected since any factor which increases the electron density at the site of the reduction would make it more difficult to add electrons.

As shown by entries 1–5 in Table IV, the correlation between $E_{1/2}$(RED) and σ_m[10] for series I is poor at pH 6.0 and 8.0, good at pH 9.2, and excellent at pH 2.2 (Figure 1) and 4.0. The precision obtainable for the polarographic reduction potential, based upon the present study, is approximately ± 0.005 V and the uncertainty in σ_m is approximately ±0.01, so that the estimated standard deviations agree fairly well with the values of s at pH 2.2 and 4.0.

As shown by entries 16–20 in Table V, the correlation between $E_{1/2}$(RED) and σ_p for series II is good at pH 8.0, slightly better at pH 2.2 (Figure 2), 4.0, and 6.0, and excellent at pH 9.2. The least significant correlations between $E_{1/2}$(RED) and σ for both series I and II occur at pH 6.0 and 8.0. Entries 21–25 for series II in Table V show that at low pH there are better correla-

(10) H. H. Jaffé, *Chem. Rev.*, **53**, 222 (1953).
(11) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

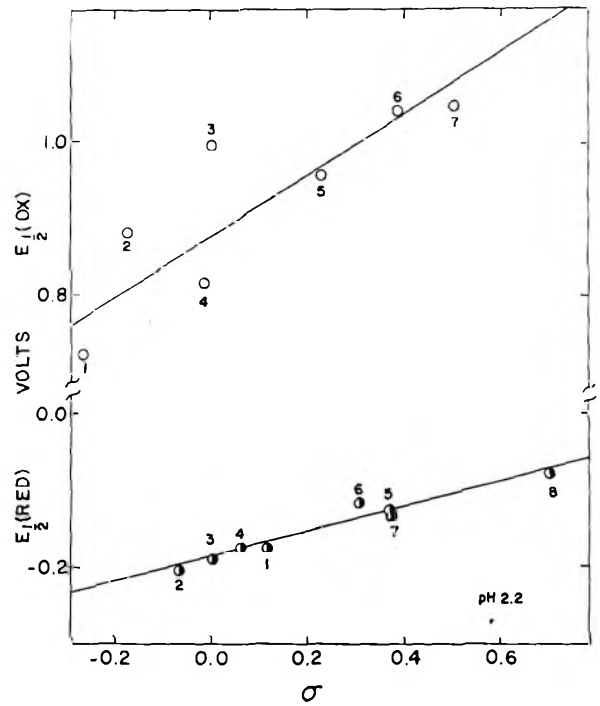

Figure 1.—The relationship between $E_{1/2}$(RED) and σ_m (◑) and between $E_{1/2}$(OX) and σ_p (○) for 4-substituted 2-nitrophenols (I). Numbers refer to compounds as listed in Table I.

TABLE IV

REGRESSION ANALYSIS DATA FOR $E_{1/2}$ *vs.* σ FOR 4-SUBSTITUTED 2-NITROPHENOLS (I)

Entry	pH	$E_{1/2}^0$[b]	ρ[c]	r[d]	s[e]	% confidence level[f]
	$E_{1/2}(\mathrm{RED}) = E_{1/2}^0(\mathrm{RED}) + \rho\sigma_m$, $n = 8$[a]					
1	2.2	−0.192	0.160	0.984	0.008	>99.95
2	4.0	−0.288	0.145	0.944	0.014	>99.95
3	6.0	−0.415	0.114	0.765	0.027	97.3
4	8.0	−0.576	0.121	0.597	0.045	88.2
5	9.2	−0.726	0.162	0.856	0.027	99.3
	$E_{1/2}(\mathrm{OX}) = E_{1/2}^0(\mathrm{OX}) + \rho\sigma_p$, $n = 7$[a]					
6	2.2	0.890	0.360	0.844	0.072	98.3
7	4.0	0.766	0.359	0.836	0.074	98.1
8	6.0	0.625	0.449	0.920	0.060	99.7
9	8.0	0.555	0.559	0.919	0.075	99.7
10	9.2	0.559	0.640	0.934	0.077	99.8
	$E_{1/2}(\mathrm{OX}) = E_{1/2}^0(\mathrm{OX}) + \rho\sigma_p^{\pm}$, $n = 7$[a]					
11	2.2	0.914	0.197	0.909	0.056	99.5
12	4.0	0.790	0.196	0.903	0.058	99.5
13	6.0	0.656	0.236	0.953	0.046	99.9
14	8.0	0.593	0.298	0.966	0.049	>99.95
15	9.2	0.603	0.337	0.969	0.053	>99.95

[a] Number of experimental points used. [b] Regression intercept. [c] Regression slope. [d] Linear correlation coefficient. [e] Standard deviation from regression. [f] Based on Student's t test (ref 13).

tions between $E_{1/2}$(RED) and exalted substituent constants, $\sigma_p^{\pm}$, which indicates that for this series resonance effects may be of substantial importance (Figure 3). Moreover, the values of s obtained at pH 2.2 and 4.0 are in fair agreement with those expected from the experimental errors thought to be present and are similar to the results for series I.

The effect of pH upon the reduction of the compounds involved is complicated, but the good correlations obtained at low pH appear to accompany the small, nearly parallel variation of $E_{1/2}$(RED) with pH for pH 2.2 and 4.0.[9]

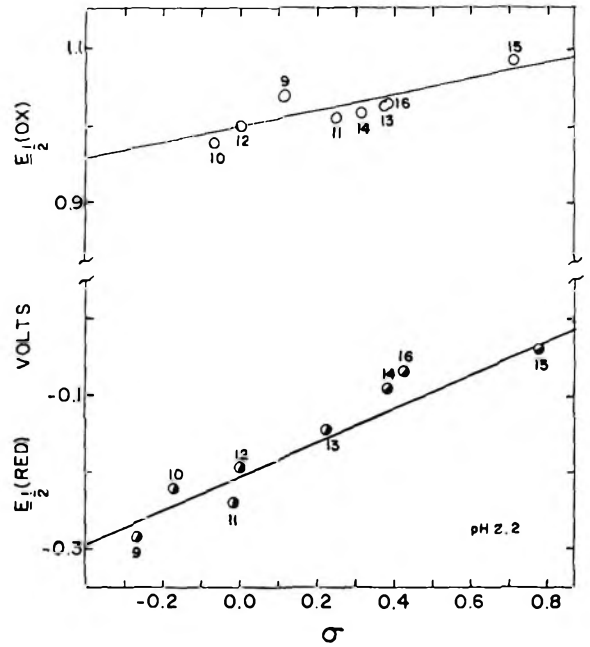

Figure 2.—Relationships between $E_{1/2}$(RED) and σ_p (◑) and between $E_{1/2}$(OX) and σ_m (○) for 5-substituted 2-nitrophenols (II). Numbers refer to compounds as listed in Table II.

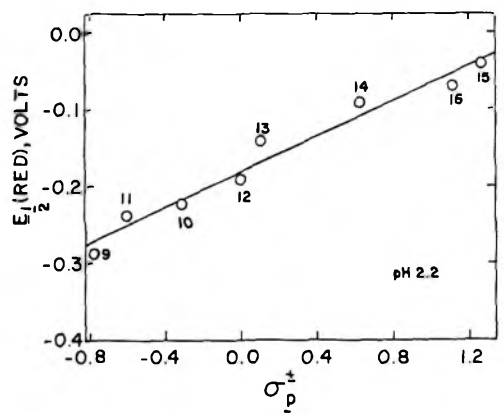

Figure 3.—The relationship between $E_{1/2}$(RED) and $\sigma_p^{\pm}$ for 5-substituted 2-nitrophenols (II). Numbers refer to compounds as listed in Table II.

The polarographic oxidation of the compounds of both series can probably best be described as the oxidation of the –OH or $-O^-$ group by loss of electrons from the molecule as the first step.[9] Plots of $E_{1/2}$(OX) *vs.* log $(i_d - i)/i$ revealed that these reactions are irreversible. It was assumed, however, that corresponding electrochemical reactions are taking place in all cases since these oxidation reactions, like the reductions, follow Zuman's[9] criteria for the validity of such assumptions. The magnitude of the potential required for oxidation decreases with increasing pH (Tables I and II), and substituents which decrease the electron density on the hydroxyl group increase the potential required for oxidation while those which increase the electron density lower the potential required for oxidation (Figures 1, 2, and 4).

The effect of pH upon oxidation is complicated, but the good correlations obtained at high pH appear to accompany the small variation of $E_{1/2}$(OX) with pH for pH 8.0 and 9.2.[9] Also, the poor correlations at the more acidic pH 2.2 and 4.0 may be partly due to the

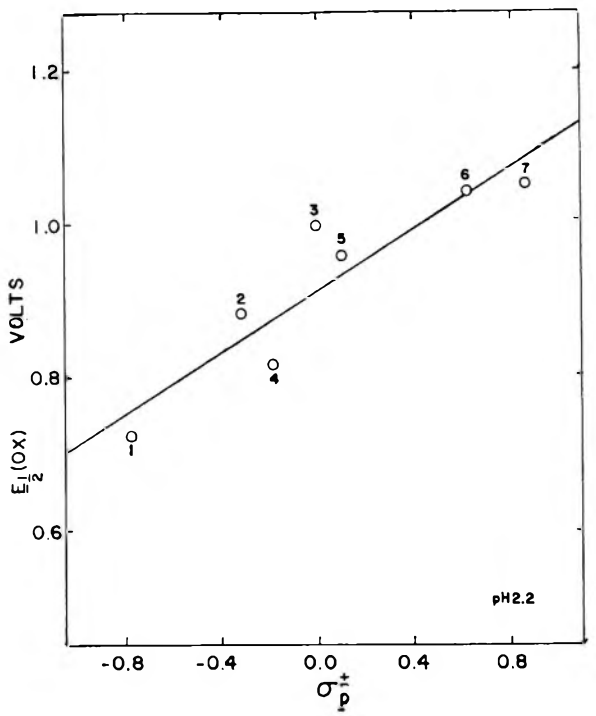

Figure 4.—Relationship between $E_{1/2}$(OX) and $\sigma_p^{\pm}$ for 4-substituted 2-nitrophenols (I). Numbers refer to compounds as listed in Table I.

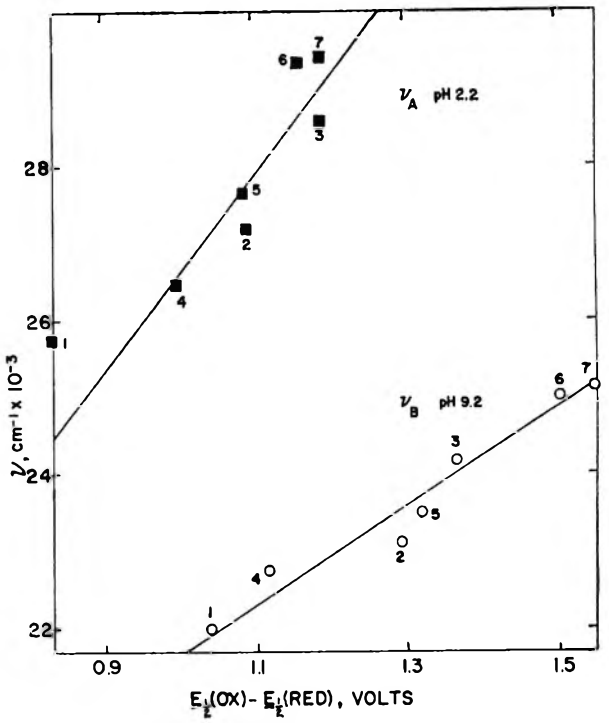

Figure 5.—The relationship between ν_A and [$E_{1/2}$(OX) − $E_{1/2}$(RED)] (■) and between ν_B and [$E_{1/2}$(OX) − $E_{1/2}$(RED)] (○). Numbers refer to compounds as listed in Table I.

TABLE V

REGRESSION ANALYSIS DATA FOR $E_{1/2}$ *vs.* σ FOR 5-SUBSTITUTED 2-NITROPHENOLS (II)

Entry	pH	E^0 [b]	ρ [c]	r [d]	s [e]	% confidence level [f]
		$E_{1/2}$(RED) = $E_{1/2}^0$(RED) + $\rho\sigma_p$, n = 7 [a]				
16	2.2	−0.204	0.229	0.968	0.023	>99.95
17	4.0	−0.293	0.236	0.974	0.022	>99.95
18	6.0	−0.424	0.253	0.966	0.027	>99.95
19	8.0	−0.583	0.289	0.946	0.039	99.9
20	9.2	−0.730	0.344	0.987	0.022	>99.95
		$E_{1/2}$(RED) = $E_{1/2}^0$(RED) + $\rho\sigma_p^{\pm}$, n = 7 [a]				
21	2.2	−0.179	0.118	0.985	0.016	>99.95
22	4.0	−0.267	0.120	0.985	0.016	>99.95
23	6.0	−0.396	0.129	0.975	0.023	>99.95
24	8.0	−0.551	0.139	0.900	0.053	99.4
25	9.2	−0.692	0.165	0.942	0.046	99.9
		$E_{1/2}$(OX) = $E_{1/2}^0$(OX) + $\rho\sigma_m$, n = 8 [a]				
26	2.2	0.997	0.103	0.856	0.017	99.3
27	4.0	0.859	0.102	0.790	0.021	98.0
28	6.0	0.683	0.211	0.899	0.028	99.8
29	8.0	0.587	0.352	0.949	0.031	>99.95
30	9.2	0.585	0.385	0.921	0.044	99.9

[a] Number of experimental points used. [b] Regression intercept. [c] Regression slope. [d] Linear correlation coefficient. [e] Standard deviation from regression. [f] Based on Student's t test (ref 13).

difficulty in measuring the half-wave potentials, since at these pH's the limiting current of the polarographic waves is very near the decomposition potential of the solvent. For series I, there is a better correlation between $E_{1/2}$(OX) and $\sigma_p^{\pm}$ (Table IV, entries 11–15) than between $E_{1/2}$(OX) and σ_p (Table IV, entries 6–10), indicating that resonance effects are important (Table IV, Figures 1 and 4). The oxidation potentials are reproducible to within ±0.015 V.

It can be generally concluded that good correlations exist between $E_{1/2}$ and σ for series I and II and that these correlations will fairly well predict new $E_{1/2}$ values from known σ values for other members of series I and II. The results show that the predictions for $E_{1/2}$(RED) are likely to be more reliable than those for $E_{1/2}$(OX) and that the uncertainty in the predicted values depends appreciably upon pH.

Correlation of Polarographic Oxidation and Reduction Half-Wave Potentials with Electronic Spectra.—If the polarographic oxidation and reduction half-wave potentials are linearly related to the ground and first excited states, respectively, then the difference [$E_{1/2}$(OX) − $E_{1/2}$(RED)] should be proportional to the energy required to raise an electron from the ground state to the first excited state, and it was hoped that a good correlation could be found between [$E_{1/2}$(OX) − $E_{1/2}$(RED)] and the frequency of the longest wavelength electronic absorption maximum.

For series I, there are good correlations between the acidic and basic electronic absorption frequencies,[4] ν_A and ν_B, and the difference in the oxidation and reduction potentials at the five pH's as shown in entries 31–35 of Table VI and in Figure 5. The standard deviations in entries 33–35 in Table VI are better than would be expected from the uncertainties in the measurements of the absorption frequencies (442 cm^{-1} acidic, 367 cm^{-1} basic) and the uncertainties in the measurements of the oxidation and reduction half-wave potentials.

The effect of substituents on the energies of the ground and excited states can be seen in Figure 1 where both oxidation and reduction half-wave potentials have been plotted on the same graph *vs.* the normal σ values. It is evident from Figure 1 that the difference in the energies of the ground and excited states increases with an increase in electron withdrawal. Also the ground-state energy seems to be affected to a greater degree by electron withdrawal than the excited state.

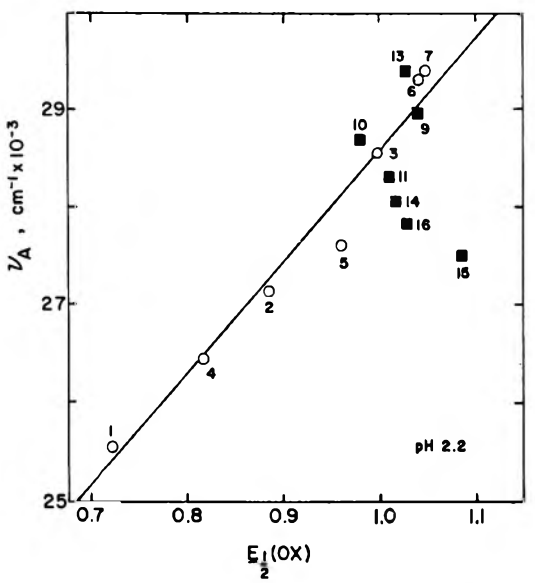

Figure 6.—Relationship between ν_A and $E_{1/2}$(OX) for 4-substituted 2-nitrophenols (○) and 5-substituted 2-nitrophenols (■). Numbers refer to compounds as listed in Tables I and II.

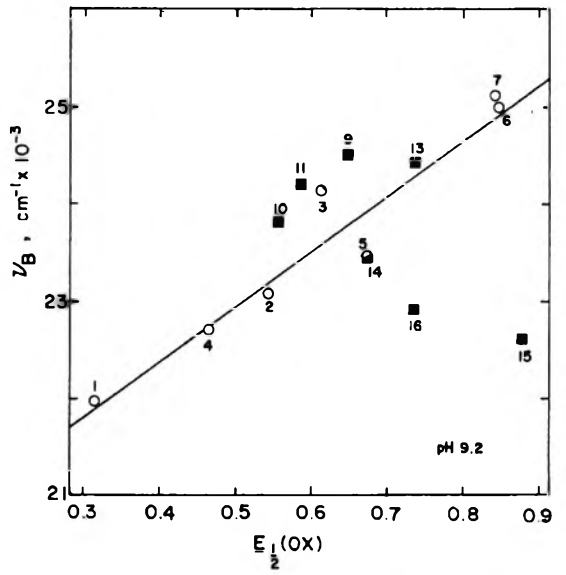

Figure 7.—Relationship between ν_B and $E_{1/2}$(OX) for 4-substituted 2-nitrophenols (○) and for 5-substituted 2-nitrophenols (■). Numbers refer to compounds as listed in Tables I and II.

TABLE VI

REGRESSION ANALYSIS DATA FOR ν *vs.* $[E_{1/2}(OX) - E_{1/2}(RED)]$ AND ν *vs.* $[E_{1/2}(OX)]$ FOR 4-SUBSTITUTED 2-NITROPHENOLS (I)

Entry	pH	ν	ν^0 [b]	C [c]	r [d]	s [e]	% confidence level [f]
		$\nu = \nu^0 + C[E_{1/2}(OX) - E_{1/2}(RED)]$, $n = 7$ [a]					
31	2.2	ν_A	13,903	12,703	0.954	479	99.9
32	4.0	ν_A	13,617	13,284	0.957	461	99.9
33	6.0	ν_A	15,872	11,174	0.985	278	>99.95
34	8.0	ν_B	16,417	6,214	0.987	205	>99.95
35	9.2	ν_B	15,232	6,388	0.982	243	>99.95
		$\nu = \nu^0 + C[E_{1/2}(OX)]$, $n = 7$ [a]					
36	2.2	ν_A	16,916	11,707	0.983	295	>99.95
37	4.0	ν_A	18,421	11,637	0.981	307	>99.95
38	6.0	ν_A	21,006	10,069	0.965	416	>99.95
39	8.0	ν_B	19,677	6,532	0.968	320	>99.95
40	9.2	ν_B	20,073	5,771	0.964	341	>99.95

[a] Number of experimental points used. [b] Regression intercept. [c] Regression slope. [d] Linear correlation coefficient. [e] Standard deviation from regression. [f] Based on Student's t test (ref 13).

This finding is in accord with the theoretical discussion of Matsen[12] for monosubstituted benzenes.

The correlation of ν_A or ν_B with $E_{1/2}$(RED) or $E_{1/2}$(OX) alone for series I is rather surprising. The correlations[13] with $E_{1/2}$(RED) are not significant, but those with $E_{1/2}$(OX) are good as shown by entries 36–40 in Table VI and by Figures 6 and 7 at pH 2.2 and 9.2. The regression lines drawn in Figures 6 and 7 are for entries 36 and 40 of Table VI and apply only to the seven members of series I (open circles). The shaded squares in these figures apply to members of series II and are plotted only for ready comparison.

Thus, for series I, it appears that the correlations of ν_A with $E_{1/2}$(OX) alone at low pH are actually superior to those of ν_A with $[E_{1/2}(OX) - E_{1/2}(RED)]$.

For series II, there are no significant correlations between $E_{1/2}$(OX), $E_{1/2}$(RED), or $[E_{1/2}(OX) - E_{1/2}(RED)]$ and absorption frequencies, with or without the inclusion of the 5-NO_2 and 5-CHO compounds. The graphical display of ν_A and ν_B *vs.* $[E_{1/2}(OX) - E_{1/2}(RED)]$ at pH 2.2 and 9.2, respectively, for all data for I and II, are given in Figures 8 and 9. The regression lines shown are for the data of I only. The data for II appear to scatter around the regression lines calculated for I, and it seems clear that some important effects are unaccounted for in II compared to I. There are four points that deviate greatly from the regression lines shown. These are for substituents 5-OCH_3 and 5-CH_3CONH in acid solution, and 5-CHO and 5-NO_2 in basic solutions. An examination of the spectral results available[5] shows that the extinction coefficients for the 5-OCH_3 and 5-CH_3CONH compounds are anomalously large in acid solution, which may indicate that these compounds do not belong to the same spectral series as the others. As mentioned above, the diffusion current for the 5-CHO compound in reduction differs from that of any of the others obtained, and there is perhaps an ambiguity in the reduction process for the 5-NO_2 compound, but the very large deviations observed in basic solutions are not present in acid solution. Moreover, the deviations appear to be in the wrong direction if the reduction processes in these materials occur at $E_{1/2}$(RED) values that are smaller in magnitude than expected from the appropriate regression analyses.

In the graphs of ν *vs.* $E_{1/2}$(OX) (Figures 6 and 7, dark squares) for series II the most widely divergent points are the 5-CHO and 5-NO_2 compounds. These are the same points which deviate the most in the graphs of ν *vs.* $[E_{1/2}(OX) - E_{1/2}(RED)]$. These deviations cannot be explained since there is no reason to suspect that the oxidations or the spectra for these compounds are anomalous.

Thus, the correlations of spectral frequencies ν_A and ν_B with the appropriate values of $[E_{1/2}(OX) - E_{1/2}(RED)]$ or $E_{1/2}$(OX) alone appear to be satisfactory for series I, but not for series II, and further studies on other series of compounds are needed in order to in-

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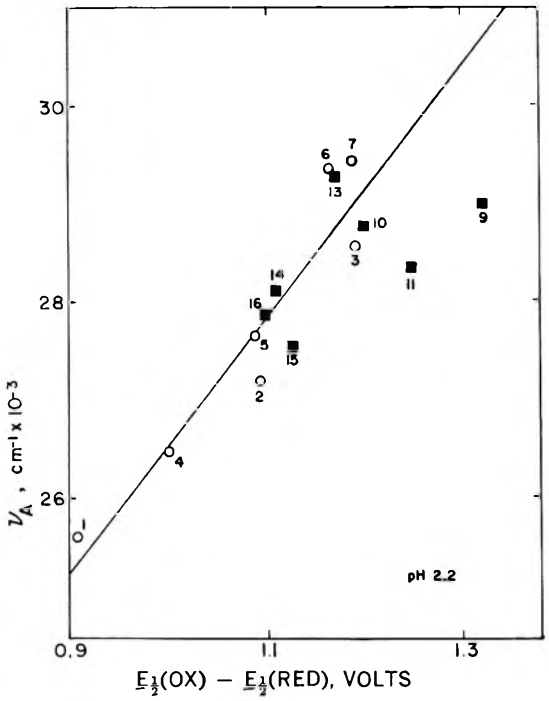

Figure 8.—Relationship between ν_A and [$E_{1/2}$(OX) − $E_{1/2}$(RED)] for 4-substituted 2-nitrophenols (○) and for 5-substituted 2-nitrophenols (■). Numbers refer to compounds as listed in Tables I and II.

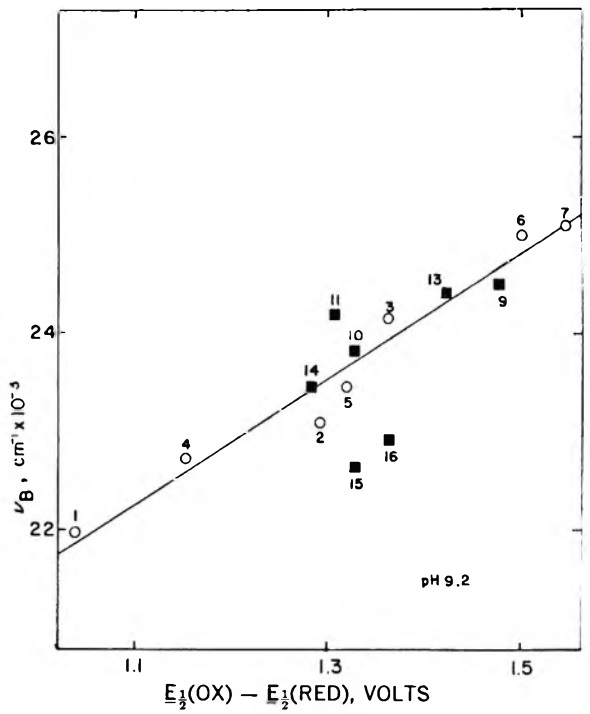

Figure 9.—Relationship between ν_B and [$E_{1/2}$(OX) − $E_{1/2}$(RED)] for 4-substituted 2-nitrophenols (○) and for 5-substituted 2-nitrophenols (■). Numbers refer to compounds as listed in Tables I and II.

vestigate these internal correlations of different measured properties of similar molecules.

Experimental Section

Materials.—The 4- and 5-substituted 2-nitrophenols used in this study were prepared and purified as reported previously.[4,5]

USP reagent quality absolute ethanol was used. Aqueous MacIlvane buffer solutions[14] (pH 2.2, 4.0, 6.0, 8.0) were prepared from reagent grade materials and water which had been deionized by passage through an Ilco Way universal deionizing column.[15] An aqueous Clark and Lub[14] buffer (pH 9.2) was prepared from deionized water and reagent grade boric acid and sodium hydroxide.

Commercially available spectrographic quality graphite rods[16] (1/8-in. diameter) were used as indicating electrodes for measuring the oxidation potentials.

Deionized water, triply distilled mercury, and reagent grade mercurous chloride and potassium chloride were used to prepare the saturated calomel reference electrode[17] (sce). Triply distilled mercury was also used in the dropping mercury indicating electrode (dme).

Measurement of Polarographic Half-Wave Potentials.—A 0.00025 *M* solution in buffered 10 vol % aqueous ethanol of a substituted 2-nitrophenol was prepared by dilution of 5 ml of a 0.0025 *M* solution in absolute ethanol to 50 ml with the appropriate buffer. (Owing to low solubility of 4-phenyl-2-nitrophenol, the 0.00025 *M* solution was prepared in buffered 30 vol % aqueous ethanol.) A 25-ml portion of solution (25°) and 6 drops of maximum suppressor (2 vol % aqueous Triton X-100) were placed in the appropriate compartment of an H-type cell with an sce in the other compartment. The solution (25°) was purged for 10 min with dry nitrogen saturated with vapor from 10 vol % aqueous ethanol and the polarographic half-wave potential was measured with a Metrohm Polarecord Model E 261 polarograph.

For the polarographic reduction half-wave potentials, the dme, as indicating electrode, was placed in the test solution with the capillary tip 0.25 in. beneath the surface, and the potentials were measured at a pressure of 52 cm with a drop time of 3.2 sec. For the system studied, the dme has a usable range (pH dependent) to −2.1 V.

For the polarographic oxidation half-wave potential, a sharpened graphite electrode[18] was used as the indicating electrode. This electrode was inserted through a one-hole rubber stopper and placed so that the tip extended 1/8 in. below the surface of the solution. It was necessary to renew the tip of the electrode after each run since, unless this was done, the wave heights decreased in successive runs of the same solution. (This effect was probably caused by contamination of the electrode surface.) Other details of the solution, apparatus, and procedure were the same as above for the polarographic reduction. For the system studied, the graphite electrode has a usable range to +1.1 V.

The half-wave potentials were determined by the point method.[19] The polarograms were of the standard "S" shape and no maxima were observed.

The diffusion currents, which are dependent on concentration and electrode surface area, could be accurately measured and reproduced for the reduction waves. However, for the oxidation waves, the surface area of the electrode varied from run to run, and therefore the diffusion currents also varied.

Reduction half-wave potentials were reproducible to ±0.005 V while the oxidation half-wave potentials were reproducible to ±0.015 V. The polarograph was checked for accuracy by determining the reduction half-wave potential of Pb^{2+} (0.005 *M* lead nitrate) in 0.1 *M* aqueous potassium chloride solution. The value of 0.396 V obtained agrees satisfactorily with that of 0.40 V reported previously.

Registry No.—Table I—1, 1568-70-3; 2, 119-33-5; 3, 88-75-5; 4, 885-82-5; 5, 89-64-5; 6, 99-42-3; 7, 6322-56-1; 8, 51-28-5; Table II—9, 704-14-3; 10, 700-38-9; 11, 712-34-5; 13, 611-07-4; 14, 713-52-0; 15, 329-71-5; 16, 704-13-2.

Acknowledgment.—This study was supported in

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(16) United Carbon Products Co., Bay City, Mich.
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part by a research grant from the Robert A. Welch Foundation and by a fellowship for P. Y. R. from the National Aeronautics and Space Administration. The statistical calculations were performed by the Data Processing Center, Texas Engineering Experiment Station, College Station, Texas 77843. We wish to thank a reviewer who brought to our attention the newer value of σ_p available for CHO.

The Spontaneous Hydrolysis of Sulfonyl Fluorides[1]

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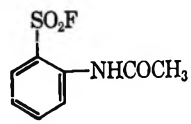
The rates of spontaneous hydrolyses of substituted benzenesulfonyl fluorides in dioxane–water (40:60 v/v) at 45.0 or 65.5° follow the sequence *o*-CH_3CONH > *p*-NO_2 > *m*-NO_2 > *o*-NO_2 > *p*-Br > *m*-CH_3CONH > H. The hydrolyses were too slow to be followed when the substituent was *p*-CH_3O, *o*-NH_2, *p*-NH_2, or *p*-CH_3CONH. The substituent effects are generally very similar to, but larger than, those found for sulfonyl chlorides and $\rho \cong 1.8$. The relatively rapid hydrolysis of *o*-acetamidobenzene sulfonyl fluoride is accompanied by loss of the acetyl group, suggesting that a neighboring-group participation of the acetamido group gives an unstable intermediate.

Sulfonyl fluorides are generally unreactive toward acidic and neutral water and hydroxylic solvents;[3-5] for example, Swain and Scott showed that benzenesulfonyl fluoride was much less reactive (by a factor of *ca.* 5×10^3) than the corresponding chloride, although it reacted readily with hydroxide ion.[5] The results were explained in terms of the strong S–F bond and the strong electron withdrawal by fluorine. However, azo dyes derived from *p*-aminobenzenesulfonyl fluoride react readily with cellulose, cellulose acetate, and some synthetic fibers.[6] In addition, Baker and his coworkers have shown that some sulfonyl fluorides are very effective enzyme inhibitors, and that the sulfonyl group is bound irreversibly near to the active site.[7] Moreover enzymes catalyzed the hydrolysis of some sulfonyl fluorides,[8] and Baker suggested that these nucleophilic attacks upon sulfonyl fluorides occur with assistance from a hydrogen-bonding donor which assists S–F bond breaking. This hydrogen-bonding donor could be an external water molecule or a protic group in the enzyme, and the nucleophile could be a group in the enzyme or an external water molecule. The fact that the hydrolysis of acyl fluorides, but not chlorides, is acid catalyzed[9] suggests that a general acid or a proton assists departure of the fluoride but not the chloride ion in water.

The aim of the present work was to examine structural effects upon the rate of the spontaneous hydrolysis of arylsulfonyl fluorides because the solvolyses of the corresponding chlorides have been studied in great detail, and all the evidence points to nucleophilic attack in the rate-limiting step although there is question as to the relative importance of bond making and breaking.[10-13] The unreactivity of the arylsulfonyl fluorides prevented our studying, quantitatively, compounds containing electron-donating groups. In addition we examined the hydrolysis of *o*-acetamidobenzenesulfonyl fluoride (I), because a derivative of this compound has been found to be surprisingly reactive to water whereas compounds derived from *m*-acetamidobenzenesulfonyl fluoride showed no such reactivity.[14]



I

Experimental Section

Materials.—The following sulfonyl fluorides were obtained commercially and were recrystallized from ethanol–water: *o*-aminobenzene (Aldrich), mp 62–64° (lit.[15] 64–65°); *p*-aminobenzene (Aldrich), mp 70–71° (lit.[15] 70°); *p*-acetamidobenzene (Aldrich), mp 175–177° (lit.[15] 174–176°); *m*-nitrobenzene (Alfred Bader), mp 46–47° (lit.[15] 46–48°). The other sulfonyl fluorides were prepared by refluxing the chlorides with KF in aqueous dioxane for 0.5–1 hr or by acylating the aminosulfonyl fluoride.[3,14] The reaction solution was poured into cold water, the liquid sulfonyl fluorides were extracted, usually into ether, the organic layer was washed with water and then dried, and the fluoride was distilled *in vacuo*. The solid fluorides were removed by filtration and recrystallized from methanol–water, ethanol–water, or benzene. The sulfonyl fluorides prepared from the chloride with fluoride ion had the following physical properties: benzenesulfonyl fluoride, bp 60–61° (1.5 mm) [lit.[5] 83° (3 mm)]; *o*-nitro-, mp 52–54° (lit.[16] 55–58°); *p*-nitro-, mp 75–78° (lit.[11] 77–79°); *p*-methoxy-, bp 103–105° (1.7 mm) [lit.[16] 175° (60 mm)]; *p*-bromo-, mp 65–66° (lit.[17] 65–66°). The infrared spectrum of the *p*-bromo compound was very similar to that in the literature.[18] *o*- and *m*-acetamidobenzenesulfonyl fluorides were

(1) Support of this work by the National Science Foundation is gratefully acknowledged.

(2) To whom inquiries should be addressed.

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prepared by acetylation of the amine using acetic anhydride in chloroform.[14] *o*-Acetamidobenzenesulfonyl fluoride recrystallized from benzene–methyl ethyl ketone had mp 99–101°. *Anal.* Calcd for $C_6H_6FNO_2S$: C, 44.2; H, 3.7; N, 6.4. Found: C, 44.3; H, 3.8; N, 6.2. *m*-Acetamidobenzene sulfonyl fluoride recrystallized from benzene had mp 114–116° (lit.[14] 114–116°).

Dioxane was purified by treating it with aqueous HCl and then with KOH, refluxing it over sodium, and then redistilling it over sodium.[19] It was stored under N_2 at 6°. Distilled and deionized water was used. Solutions of lanthanum nitrate (MCB) were standardized against KF.

The kinetic solvent was dioxane–water, 40:60 v/v, made up by weight from known densities, using redistilled and deionized water.

Kinetics.—The reaction was followed by determining fluoride ion by titration with lanthanum nitrate (0.03 *N*) using a specific fluoride ion electrode (Orion 94–09). Aliquots (5–10 ml) of the reaction mixture were diluted with cold ethanol[20] (10 ml), and the pH was brought to 6–7 with 0.022 *M* NaOAc. Polyethylene beakers and pipets were used, and the end point was taken as the point of inflection of a plot of millivolts *vs.* milliliters of titrant. Because the reactions were very slow, infinity titers were obtained by adding sodium hydroxide with which the fluorides rapidly react.[5]

The choice of suitable reaction vessels was a major problem. Polyethylene bottles were satisfactory for use at 45° provided that the caps were fitted with Viton O rings, but they failed at high temperatures after *ca.* 24 hr. Polycarbonate bottles were slightly better and lasted for *ca.* 36 hr, but we finally found that Teflon bottles made satisfactory containers. Generally the screw caps gave satisfactory seals, but sometimes it was necessary to use Teflon liners. Every bottle was tested for evaporation of the kinetic solvent under reaction conditions.

The hydrolyses of the more reactive sulfonyl fluorides were followed for two half-lives, but generally the reactions were so slow that we could only follow them for one half-life, and reactions of *p*-acetamidobenzene sulfonyl fluoride were followed for only *ca.* 30% reaction. The first-order rate constants, k_ψ, are in sec^{-1}.

Reaction Products.—Because of the possibility that hydrolysis of *o*-, *m*- and *p*-acetamidobenzenesulfonyl fluorides might be accompanied by anilide hydrolysis, we took reaction mixtures after *ca.* two half-lives of reaction of the *ortho* compound and treated portions of them at 0° with $NaNO_2$ until starch–iodide paper gave a positive test. The solution was then treated with β-naphthol in NaOH.[22] The copious crop of red crystals obtained from the *ortho* compound was recrystallized from aqueous EtOH. *Anal.* Calcd for $C_{16}H_{11}N_2O_4SNa \cdot 0.5H_2O$: C, 53.5; H, 3.4; N, 7.8. Found: C, 53.8; H, 3.6; N, 7.6. When this test was carried out with *m*- and *p*-acetamidobenzenesulfonyl fluorides there was only a slight coloration of the solution. The results suggested that the anilide group was lost during the reaction of *o*-acetamidobenzenesulfonyl fluoride, and we examined the nmr spectrum of a 10% solution of the substrate in dioxane–D_2O, 40:60 v/v after various times at 65.5°, using 1% DSS as an internal standard. The methyl protons of the acetamido group have δ 2.20 (relative to DSS), but, as the reaction proceeds, this peak decreases and a new peak δ 2.25 appears, which is identical with that of added acetic acid.

Results

The first-order rate constants are given in Table I and the activation parameters, where available, are in Table II. These parameters are in the range expected for a bimolecular reaction for which bond making predominates in the transition state. For reactions which can be followed only to a partial extent, reaction order cannot be determined from linearity of plots based on the integrated first-order rate equation. However, the spread of independently determined values of k_ψ was generally less than 10% for twofold changes in substrate concentration, showing that first-order kinetics are followed and confirming the earlier evidence against hydrogen ion catalysis in dilute acids.[3-5] The only exception was the hydrolysis of *p*-acetamidobenzenesulfonyl fluoride where at 65.5° $k_\psi \approx 1 \times 10^{-7}$ sec^{-1} with 0.01 *M* substrate and $\approx 0.5 \times 10^{-7}$ sec^{-1} with 0.015 *M* substrate. These latter values were based on the first 10–30% of the reaction and are almost certainly unreliable because of the hydrolysis of the anilide to give the less reactive *p*-aminobenzenesulfonyl fluoride. Hydrolysis of *p*-acetamidobenzenesulfonyl fluoride was therefore not examined in detail. Hydrolysis to the amide does not appear to be a problem with the *m*-acetamido compound, and the greater electron withdrawal by a *para* compared with a *meta* sulfonyl fluoride group could be responsible for this difference. The release of fluoride from *o*-acetamidosulfonyl fluoride is much faster than anilide hydrolysis under our conditions (*cf.* ref 23).

The hydrolyses of *p*-methoxybenzene-, *p*-aminobenzene-, and *o*-aminobenzenesulfonyl fluorides were so slow that we were unable to obtain rate constants for hydrolysis of these compounds.

Table I

Spontaneous Hydrolysis[a]

Substituent	Registry no.	$10^2 C_s$, M	$10^6 k_\psi$, sec^{-1}
H	368-43-4	1.35	1.16
		2.04	1.07
m-CH_3CONH	4857-88-9	0.84	1.56
		1.11	1.57
		1.59	1.60
o-CH_3CONH	24299-90-9	0.84	6.24[b]
		1.01	6.03[b]
		1.69	6.10[b]
		0.68	30.3
		1.04	33.1
		1.26	31.1
p-Br	498-83-9	1.07	2.45
		1.98	2.53
o-NO_2	433-98-7	0.89	0.89[b]
		1.01	4.25
		1.25	4.49
m-NO_2	349-78-0	0.91	2.96[b]
		1.15	2.71[b]
		2.43	2.77[b]
		0.97	12.9
		1.13	12.6
		1.55	12.4
p-NO_2	349-96-2	1.14	5.05[b]
		1.17	4.90[b]
		2.29	5.35[b]
		0.97	22.4
		1.29	24.8
		1.60	22.5

[a] In dioxane–water, 40:60 v/v, at 65.5° unless specified. [b] 45.0°.

Table II

Activation Parameters

Substituent	ΔH^*, kcal mol^{-1}	ΔS^*, eu
o-NO_2	16.0	−40
m-NO_2	15.1	−41
p-NO_2	14.8	−41
o-CH_3CONH	16.3	−36

(19) A. I. Vogel, "Textbook of Practical Organic Chemistry," Longmans, Green and Co. Ltd., London, 1949, p 177.

(20) Ethanol increases the sensitivity of the fluoride ion electrode.[21]

(21) J. J. Lingane, *Anal. Chem.*, **39**, 881 (1967).

(22) G. Schetty, *Helv. Chim. Acta*, **49**, 461 (1966).

(23) I. Meloche and K. J. Laidler, *J. Amer. Chem. Soc.*, **73**, 1712 (1951); M. L. Bender and R. J. Thomas, *ibid.*, **83**, 4183 (1961).

Discussion

Relation between Structure and Reactivity.—The *o*-acetamido group markedly enhances the rate, but for the other compounds the rate increases with substitution of electron-attracting groups, as for hydrolysis of sulfonyl chlorides. For the sulfonyl fluorides the rate sequence (omitting the *o*-acetamido compound) is *p*-NO_2 > *m*-NO_2 > *o*-NO_2 > *p*-Br > *m*-CH_3CONH > H > *p*-CH_3CONH (Table 1), and for the chlorides it is *p*-NO_2 > *m*-NO_2 > *p*-Br > H > *o*-NO_2 > *p*-CH_3CONH.[12] For the hydrolyses of sulfonyl chlorides at 25° in 49.1% aqueous dioxane a plot of log k_ψ against σ is curved with ρ increasing from *ca.* +0.6 for σ values close to zero to *ca.* +1.2 for positive σ values.[11] For the fluorides at 65.5° in dioxane–water, 40:60 w/w, the corresponding plot is also concave, although a straight line of slope +1.8 can be drawn through the points by allowing a maximum deviation of 0.1 in log k_ψ (Figure 1). The vertical bars in Figure 1 are drawn allowing an uncertainty of ±5% in the values of k_ψ, except for k_ψ for *p*-acetamidobenzenesulfonyl fluoride (σ = 0.00) where we assume an uncertainty of ±50% (Results). The larger values of ρ suggest that electronic effects are more important for hydrolysis of the fluorides than the chlorides. Jenkins and Hambly explained the curvature in the plots of log k_ψ against σ for sulfonyl chloride hydrolysis in terms of a change in the relative importance of bond making and breaking with changes in substituent groups (*cf.* ref 24 and 25), and consistently they found that ρ decreased as the solvent was made more aqueous.

We could explain the curvature in the plots of log k_ψ against σ for sulfonyl fluorides in similar terms and assume that the larger value of $\rho \approx +1.8$ is caused by the greater importance of bond making which results from the strength of the S–F bond and the strong electron withdrawal by fluorine. However, we note that the temperature of our experiments was relatively high, and the solvent was less aqueous than that used for hydrolysis of the chlorides both of these factors tend to increase ρ.[10-12] In addition, σ may not be the appropriate substituent parameter for these reactions.[26]

The high relative reactivity of *o*-nitrobenzenesulfonyl fluoride, compared with the low reactivity of the corresponding chloride, also gives some support for the assumption that electronic effects are more important in the sulfonyl fluorides than in the chlorides and that the effect of the *o*-nitro group is electronic rather than steric.

Charton has shown that *ortho* substituents can exercise large electronic effects[27] which may be due to a resonance or to a field effect, and such electronic effects of an *o*-nitro group should be more important in hydrolysis of a sulfonyl fluoride compared with the chloride.

Effect of the *o*-Acetamido Group.—The relatively high reactivity of *o*-acetamidobenzenesulfonyl fluoride (I) cannot be caused solely by either an electronic or steric effect. For example, for *p*-acetamido σ = 0.00, for the *meta* substituent σ = 0.21, and log k_ψ for the *m*-acetamidobenzenesulfonyl fluoride fits well on a linear free energy plot, whereas the *ortho* isomer is more reactive (by *ca.* 30-fold) than expected in terms of the value of σ. In addition, comparison between *o*-, *m*-, and *p*-nitrobenzenesulfonyl fluorides suggests that a steric effect of an *ortho* group, if present, could not markedly enhance substrate reactivity.

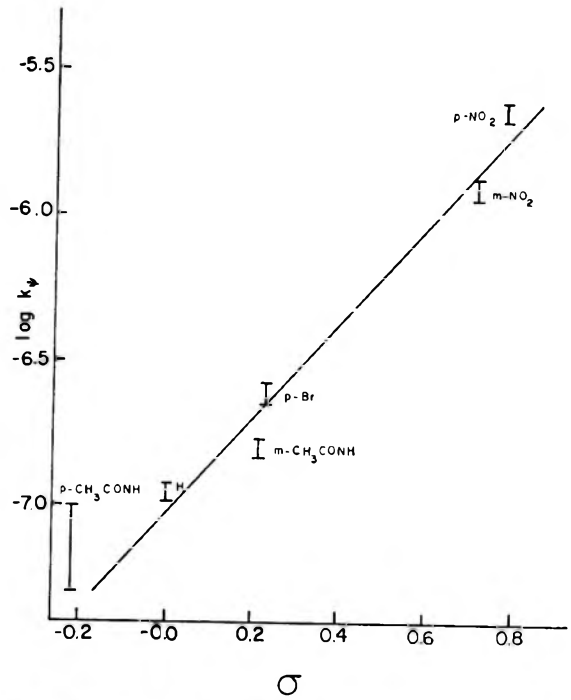
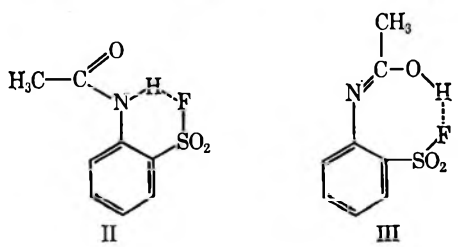


Figure 1.—Linear free energy plot for spontaneous hydrolysis.

We can eliminate hydrolysis of the acetamido residue to give *o*-aminobenzenesulfonyl fluoride, followed by its hydrolysis, as a possible mechanism. Anilides are generally unreactive except in the presence of acids or bases,[23] and neither *m*- nor *p*-acetamidobenzenesulfonyl fluoride hydrolyze rapidly to the aminobenzenesulfonyl fluoride; in addition we could detect no hydrolysis of *o*-aminobenzenesulfonyl fluoride after 2 months at 45.0° in dioxane–water 40:60 w/w.

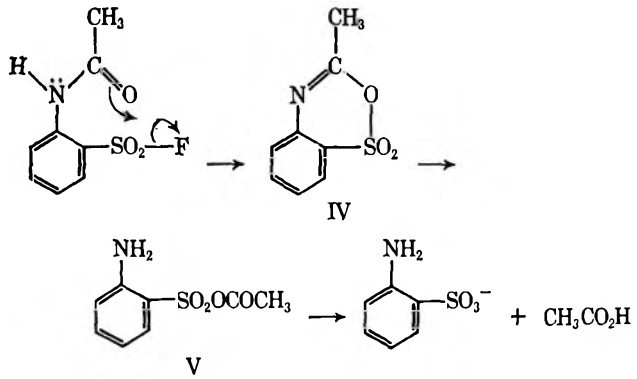
Therefore it seems that the *o*-acetamido group provides intramolecular catalysis. One possibility is that it is acting as a general acid, as in II or III.



There is evidence for hydrogen bonding to oxygen in compounds similar to II and III, *e.g.*, in *o*-acetamidobenzene sulfones and sulfonamides.[28] However, intramolecular general acid catalysis of itself can not explain the loss of the acetyl group during hydrolysis. A reasonable mechanism involves nucleophilic attack by the acetamido group upon sulfur.

(24) C. G. Swain and N. P. Langsdorf, *J. Amer. Chem. Soc.*, **73**, 2813 (1951).
(25) Y. Yukawa and Y. Tsumo, *Bull. Chem. Soc. Jap.*, **32**, 971 (1959).
(26) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, Chapter 7.
(27) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615, 619, 624, 969 (1969).
(28) J. R. Bartels-Keith and R. F. W. Cieciuch, *Can. J. Chem.*, **46**, 2593 (1968); *cf.* I. D. Rae, *ibid.*, **46**, 2589 (1968).

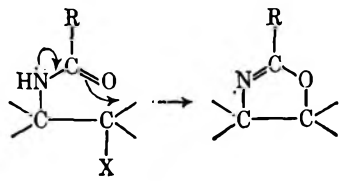
There is no nmr evidence for the existence of the intermediates IV and V, but both of them should be



very reactive under the hydrolysis conditions. This mechanism assumes that there is no intramolecular hydrogen bonding to the leaving fluoride ion which should be solvated by solvent water, and the hydrogen on the nitrogen atom is a far way from the fluoride atom in the transition state.

In this mechanism it is assumed that water molecules will solvate the departing fluoride ion and remove the amide proton. This mechanism is very similar to that proposed by Baker and his coworkers for the irreversible sulfonylation of a nucleophilic group of an enzyme by a sulfonyl fluoride.[7,8]

Amido groups provide powerful anchimeric assistance to ionization at saturated carbon,[29] and in this system the intermediate oxazoline can be isolated. In addition



intramolecular acylation of the conjugate base of an amide occurs very readily[30] by a reaction which is somewhat similar to that proposed here.

Acknowledgment.—We thank Professor B. R. Baker for helpful discussions and Mr. D. Hachey for technical assistance.

(29) S. Winstein and R. Boschan, *J. Amer. Chem. Soc.*, **72**, 4669 (1950).

(30) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitui, *ibid.*, **84**, 2421, (1962); J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); M. T. Behme and E. H. Cordes, *ibid.*, **29**, 1255 (1964).

Rearrangements of Sulfones to Sulfinic Acids *via* Carbanion Intermediates[1]

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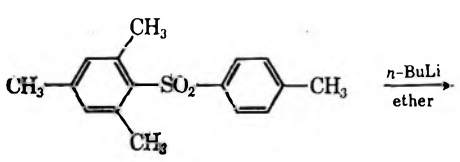
Mesityl 1-naphthyl sulfone was shown to rearrange to 2-(1′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid by treatment with *n*-butyllithium in ether, or to the 2′-naphthylmethyl isomer with potassium *t*-butoxide in dimethyl sulfoxide. In contrast, mesityl *p*-tolyl sulfone, mesityl *m*-tolyl sulfone, and mesityl *o*-tolyl sulfone were shown to rearrange to the corresponding 2-(4′-methylbenzyl)-, 2-(3′-methylbenzyl)-, and 2-(2′-methylbenzyl)-4,6-dimethylbenzenesulfinic acids, respectively, with either *n*-butyllithium in ether or potassium *t*-butoxide in dimethyl sulfoxide. Mesityl *m*-tolyl sulfone, on treatment with *n*-butyllithium in ether at 0° for a short time followed by quenching with CO_2 and subsequent decarboxylation, gave 1,5,7-trimethyl-4a,9a-dihydrothioxanthene 10,10-dioxide (**8**), the product of attack *ortho* rather than *para* to the tolyl methyl. Mesityl *o*-tolyl sulfone gave, in the same reaction, or by rapid quenching with water, 2,4,9a-trimethyl-4a,9a-dihydrothioxanthene 10,10-dioxide (**12**), resulting from ionization of the tolyl methyl. When **8** was treated with either base–solvent system, it rearranged to the same acid product as did its sulfone precursor. Sodium ethoxide in hot ethanol, however, caused **8** to rearrange to 2-(2′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid. These results are discussed in terms of the proton-donating ability of the solvent, the aromatic character of the rings, and relative acid–base strengths.

Aryl sulfones containing an *o*-methyl group have been shown to rearrange to *o*-benzylbenzenesulfinic acids when treated with *n*-butyllithium in ether,[2] or with potassium *t*-butoxide in dimethyl sulfoxide (DMSO).[3] In the conversion of mesityl *p*-tolyl sulfone (**1**) to 2-(4′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid (**2**),



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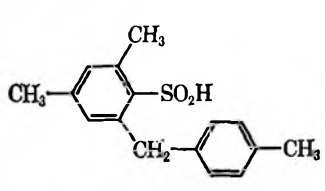


2

the rearrangement was shown to proceed *via* displacement at the carbon bearing the sulfonyl group (*i.e.*, with retained orientation on the part of the migrating group).[3] The reaction was also shown to proceed with various substituents other than methyl in the migrating benzene ring.[4]

Drozd and coworkers have shown that, if mesityl *p*-tolyl sulfone is treated with *n*-butyllithium for a short time, followed by rapid quenching, a 4a,9a-dihydrothioxanthene 10,10-dioxide can be isolated from the reaction mixture.[5] Similar results were obtained with other diphenyl sulfones.[6,7] These products must result

(1) Paper VII in the series on rearrangements of aryl sulfones.

(2) W. E. Truce, W. J. Ray, Jr., O. L. Norman, and D. B. Eickemeyer, *J. Amer. Chem. Soc.*, **80**, 3625 (1958).

(3) W. E. Truce, C. R. Robbins, and E. M. Kreider, *ibid.*, **88**, 4027 (1966).

(4) W. E. Truce and M. M. Guy, *J. Org. Chem.*, **26**, 4331 (1961).

(5) V. N. Drozd and T. Yu. Frid, *Zh. Org. Khim.*, **3**, 373 (1967).

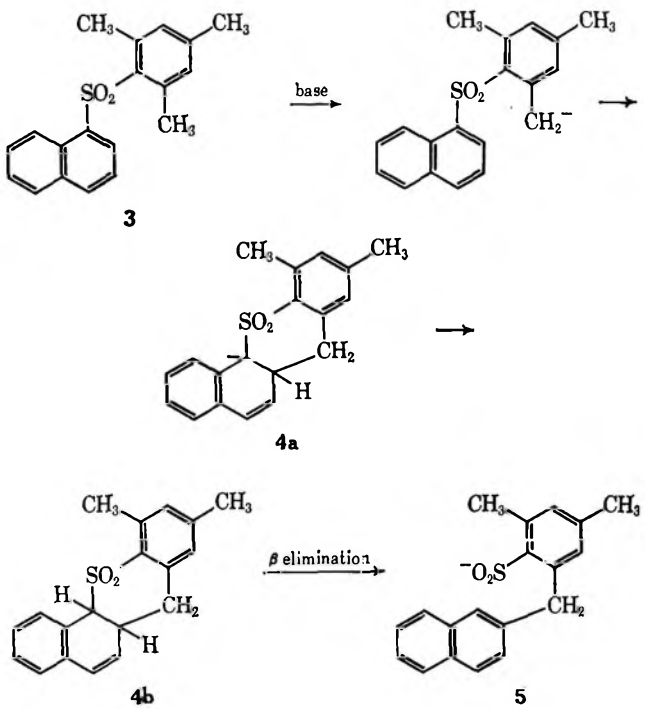
(6) V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **169**, 107 (1966).

(7) V. N. Drozd, L. I. Zefirova, and U. A. Ustynyuk, *Zh. Org. Khim.*, **4**, 1794 (1968).

from intramolecular Michael addition of the initially formed benzylic carbanion to the 1,2 bond of the other benzene ring.

Results

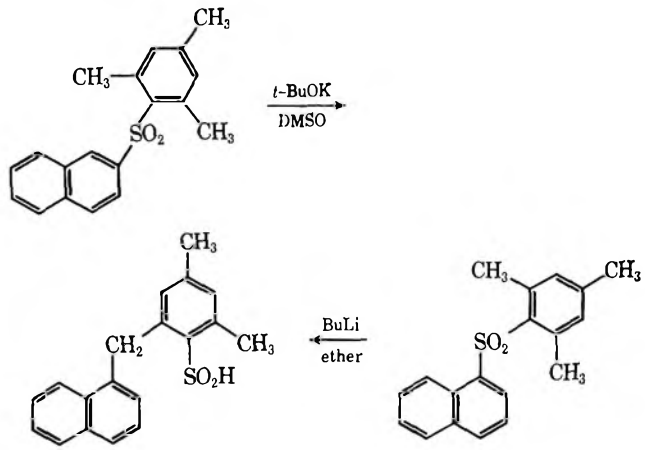
Mesityl Naphthyl Sulfones.—Previously it was shown[3] that treatment of mesityl naphthyl sulfones with potassium *t*-butoxide in DMSO resulted in rearrangement with a change in orientation on the part of the migrating naphthyl.[8] Mesityl 1-naphthyl sulfone (**3**) was rearranged under these conditions to 2-(2′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid (**5**). Similarly, mesityl 2-naphthyl sulfone rearranged to give the product with naphthyl substituted in the 1 position. The rearrangement was suggested to involve a Michael addition of the benzylic carbanion to the 1,2 bond of naphthalene, followed by a β elimination. Drozd and



3 **4a** **4b** **5**

coworkers,[9] and we,[10] independently, have been able to isolate the intermediate compound **4b** thus giving credence to this mechanism.

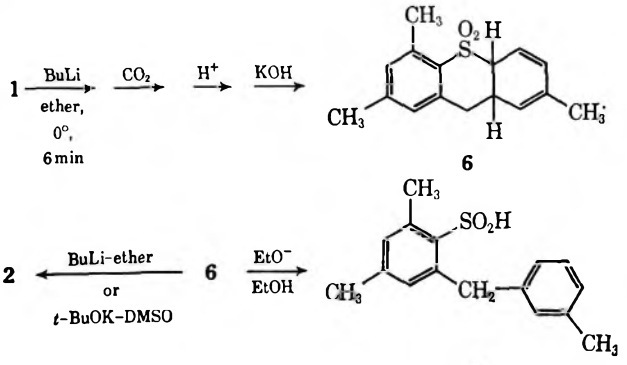
Mesityl 1-naphthyl sulfone, when treated with *n*-butyllithium in ether, gave a 42% yield of a sulfinic acid product, which was derivatized with 2-hydroxy-3,5-dichlorobenzyl chloride. This was found to be different from the derivative from the *t*-butoxide–DMSO-induced rearrangement product from mesityl 1-naphthyl sulfone, but identical (ir, melting point, and mixture melting point) with the derivative from the *t*-butoxide–DMSO-induced rearrangement product from mesityl 2-naphthyl sulfone. This product was previously shown[3] to be 2-(1′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid. Mesityl 1-naphthyl sulfone, therefore, will rearrange *via* direct displacement or addition–β elimination, depending on the base–solvent system used.



Mesityl 2-naphthyl sulfone rearranges with *n*-butyllithium in ether to the extent of only 5%. The product, sulfinic acid, was therefore not available in sufficient quantities for structure identification. Presumably this reaction also proceeds *via* direct displacement (to the extent that it occurs).

Mesityl *o*-, *m*-, and *p*-Tolyl Sulfones.—The three isomeric mesityl tolyl sulfones were prepared and rearranged under Truce–Smiles conditions to determine whether at least a small amount of a common product could be seen in the nmr of the crude sulfinic acid products arising from some addition–β elimination in the rearrangement of one or more of these sulfones with either base–solvent system. The product acids were found by nmr to be isomerically pure, however, and different from each other. Our earlier results[3] that mesityl *p*-tolyl sulfone gives the same product with either *n*-butyllithium in ether or potassium *t*-butoxide in DMSO were confirmed. It therefore appears that with the mesityl tolyl sulfones no addition–β elimination occurs under Truce–Smiles conditions.

Drozd[5,7] has isolated the cyclized product 2,5,7-trimethyl-4a,9a-dihydrothioxanthene 10,10-dioxide (**6**) from mesityl *p*-tolyl sulfone by treating the sulfone with *n*-butyllithium at 0° for a few minutes and by subsequent pouring onto CO_2, followed by decarboxylation with 10% KOH solution. This product could be caused to rearrange to **2** by treatment with *n*-butyllithium in ether or to 2-(3′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid (**7**) by treatment with sodium ethoxide in ethanol. We have also found that treatment of **6** with potassium *t*-butoxide in DMSO leads to the same product, **2**, as treatment with *n*-butyllithium in ether.



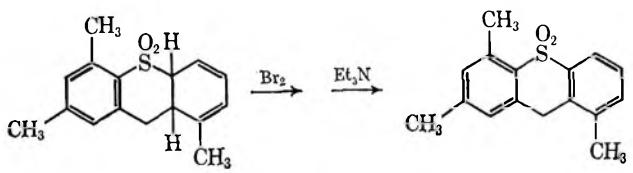
(8) Our earlier report[3] that the naphthalene compounds give the same rearrangement product with either potassium *t*-butoxide in DMSO, or with *n*-butyllithium in ether was in error. The structure proof in that paper was carried out only on the products from rearrangement with potassium *t*-butoxide in DMSO.

(9) V. N. Drozd and Kh. A. Pak, *Zh. Org. Khim.*, **3**, 2079 (1967).

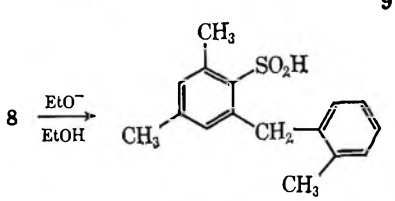
(10) E. M. Kreider, Ph.D. Thesis, Purdue University, Aug 1967.

Mesityl *m*-tolyl sulfone, when treated with *n*-butyllithium in ether, gave an 83% yield of an unstable sulfinic acid which was shown, through derivatization with 2-hydroxy-3,5-dichlorobenzyl chloride, to be identical with the acid **7**, produced from the ethoxide-induced rearrangement of **6**. In analogy to the *p*-tolyl system, mesityl *m*-tolyl sulfone was rearranged by potassium *t*-butoxide in DMSO in 82% yield to the same product, **7**, as with *n*-butyllithium in ether. The lithium salt of **7** could be isolated by filtering the butyllithium reaction mixture before hydrolysis with water. When this salt was desulfurized by treatment with aqueous $HgCl_2$ followed by removal of mercury with hot HCl in aqueous ethanol, and the resulting hydrocarbon was compared with authentic samples of 3,3′,5- and 3,4′,5-trimethyldiphenylmethanes prepared earlier by known methods,[3] the hydrocarbon was found to be identical with the 3,3′,5 isomer, but different from the 3,4′,5 isomer (ir, nmr, $n^{27}D$, and boiling point), thus indicating rearrangement with retained *meta* orientation.

The product 1,5,7-trimethyl-4a,9a-dihydrothioxanthene 10,10-dioxide (**8**) could be isolated by treatment of mesityl *m*-tolyl sulfone with *n*-butyllithium at 0° for a short time followed by carboxylation–decarboxylation. The product in which the benzyl carbanion added to the *ortho* rather than the *para* position relative to the tolyl methyl group was isolated exclusively. The structure of this product was confirmed by bromination and dehydrohalogenation to give a thioxanthene 10,10-dioxide, **9**, which was different from both the 2,4,6- and 2,4,7-trimethyl derivatives. The 2,4,6 isomer showed the hydrogen on the carbon adjacent to the carbon carrying the SO_2 (on C_5) to be a singlet in the nmr;[11] the 2,4,7 isomer showed the hydrogen on C_5 to be a doublet with J = 8.6 Hz;[11] **9**, however, had a triplet, J = 4.5 Hz, for the C_5 hydrogen. The structure of this compound was therefore assumed to be 1,5,7-trimethylthioxanthene 10,10-dioxide. This compound was also alternately synthesized from 2-(2′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid *via* a chlorination and Friedel–Crafts reaction (see below). While this work was in progress, Drozd[7] independently reported the isolation of **8** and its aromatization to **9**.



8 **9**



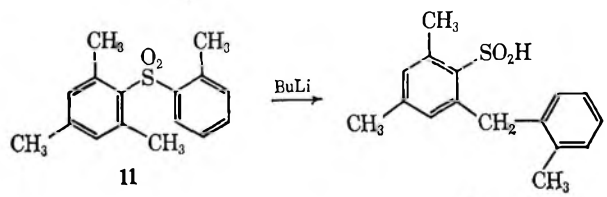
10

Further proof of the structure of the dihydro compound, **8**, was obtained when it was treated with an excess of sodium ethoxide in ethanol giving a 48% yield of a sulfinic acid. This acid was different from the *n*-butyllithium-induced rearrangement product from either *p*- or *m*-tolyl mesityl sulfone and was assumed, by analogy to the ethoxide-induced rearrangement of **6**, to be the isomeric 2-(2′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid (**10**). However, treatment of **8** with either potassium *t*-butoxide in DMSO or *n*-butyllithium in ether caused rearrangement to the same product, **7**, as was obtained by treating mesityl *m*-tolyl sulfone under the same conditions.

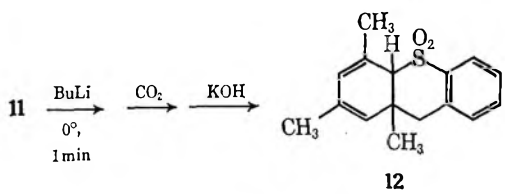
When either mesityl *p*-tolyl or mesityl *m*-tolyl sulfone was treated with an excess of sodium ethoxide in ethanol under the same conditions as were used with **6** and **8**, no acidic product resulted, and only starting sulfone could be recovered.

Treatment of mesityl *o*-tolyl sulfone (**11**) with *n*-butyllithium in ether gave a 71% yield of a fairly stable sulfinic acid. This acid was identical with **10** produced from the ethoxide-induced rearrangement of **8**. The same product, **10**, was obtained in 96% yield when **11** was treated with potassium *t*-butoxide in DMSO. The sulfinic acid **10** was treated with Cl_2 followed by cyclization with $AlCl_3$ to give a product which was identical with **9**, thus confirming its structure as 2-(2′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid. Therefore, all three of the isomeric mesityl tolyl sulfones rearrange under the Truce–Smiles conditions with retention of orientation.

When a solution of mesityl *o*-tolyl sulfone was treated with *n*-butyllithium at 0° for a short time followed by either protonation or carboxylation–decarboxylation, 2,4,9a-trimethyl-4a,9a-dihydrothioxanthene 10,10-dioxide (**12**) was the product rather than the expected



11 **10**



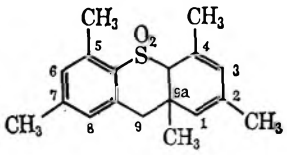
12

2,4,5- or 2,4,8a-trimethyl isomers. Only a 4% yield of **12** could be obtained from the carboxylation procedure along with 19% of the recovered starting material and 77% of the rearranged sulfinic acid, **10**. However, when the cold reaction mixture was poured directly into water, and the organic layer was dried and evaporated, 49.4% of a white solid was obtained which nmr indicated to be approximately 40% **12** and 60% starting material, thus giving a *ca.* 20% yield of **12**. None of the other two possible products was detected in the nmr.

The structure of the product was determined by analogy to the nmr of the cyclized product from dimesityl sulfone.[12] This compound has the methyl groups at C_5 and C_7 as typical aryl methyls (δ 2.29 and 2.63), the C_4 methyl at δ 2.10, the C_2 methyl at δ 1.63, and the C_{9a} methyl at δ 1.20. **12** has its methyl peaks

(11) V. N. Drozd and L. I. Zefirova, *Zh. Org. Khim.*, **4**, 165 (1968).

(12) V. N. Drozd and V. I. Scheichenko, *ibid.*, **3**, 554 (1967).



at δ 1.20, 1.55, and 2.10 in analogy to the methyls at C_{9a}, C_2, and C_4; no peaks appear in the δ 2.2–2.9 region which is the normal region for aromatic methyls. This eliminates the other two possible isomers, as well as strongly implicating the 2,4,9a-trimethyl isomer.

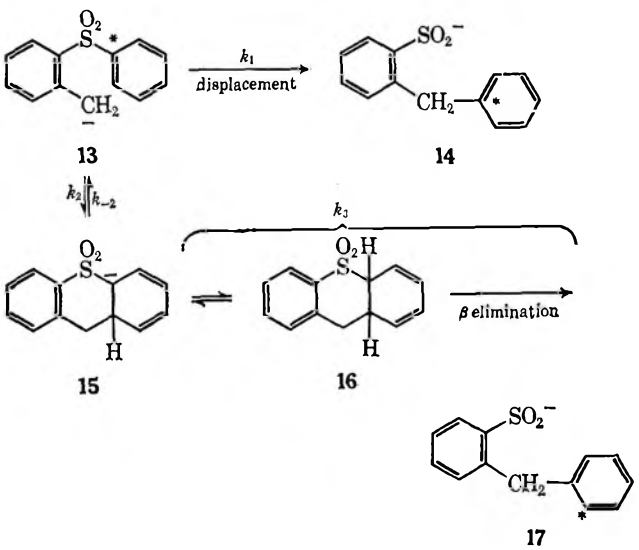
When mesityl *o*-tolyl sulfone was allowed to react with *n*-butyllithium in ether for 4.5 hr followed by pouring onto CO_2 and subsequent decarboxylation, no product precipitated, thus indicating that **12** is formed reversibly and can go on under the reaction conditions to give rearranged sulfinic acid **10**.

The fact that the only cyclization product which is isolable from the *o*-tolyl sulfone results from ionization of the tolyl methyl group, followed by addition across the α,β bond of the mesityl ring, rather than ionization of a mesityl methyl, followed by addition across the tolyl α,β bond, would seem to indicate that the cyclizations are, indeed, only side equilibria in these reactions and not intermediate steps as was suggested.[13] If these were actually intermediates, the *o*-, *m*-, and *p*-tolyl compounds which give analogous rearrangements would be expected to give analogous intermediates. Such is not the case.

Conclusions

Rearrangements of *o*-methylaryl sulfones to sulfinic acids *via* carbanion intermediates can occur by at least two mechanisms, as summarized in Scheme I, *i.e.*, (1) a direct displacement by the benzylic center on the sulfone-bearing carbon, and (2) a Michael addition–β-elimination sequence. Which pathway is followed is determined by the nature of the sulfone and the base–solvent system.

SCHEME I



In both systems, ionization (metalation) to a benzylic carbanion, **13**, is the first step. Apparently, in ether an equilibrium is set up with **15**. No proton source is available, however; so rearrangement to a sulfinic acid can only occur *via* the direct displacement reaction, regardless of the nature of the migrating ring. In DMSO, however, the solvent can act as a proton source, and the picture is more complex. Again, an equilibration between **13** and **15** is established. Which path operates, then, in DMSO is a function of the relative magnitudes of the rates k_1, and k_3, and the equilibrium constant $K = k_2/k_{-2}$. The rate constants k_1 and k_3 should not vary greatly from phenyl to naphthyl. K, however, will be greatly changed. In the equilibration between **13** and **15**, the aromaticity of phenyl or naphthyl is lost. The loss of resonance energy from one ring of the naphthyl system should be considerably less than the stabilization energy loss from a phenyl ring. This difference in energy required for the cyclization should cause the equilibrium constants, K, to differ by perhaps a factor of 10^3–10^6. This could easily be enough difference to cause a change from seeing exclusively one product (**14**) when phenyl migrates, to seeing exclusively the other product (**17**) when naphthyl migrates.

Treatment of the cyclized species **16** with various bases is simply a matter of acid and base strengths. With the very strong bases, *n*-butyllithium–ether or potassium *t*-butoxide–DMSO, the kinetically most acidic hydrogen, that α to the sulfonyl, is abstracted, leading once again to the equilibrating anions **15** and **13**, to which the above arguments apply. The weaker base, ethoxide in ethanol, is too weak to form a carbanion; therefore, a concerted β elimination is the only pathway available leading to product **17**.

Experimental Section[14]

General Procedure for the *n*-Butyllithium-Induced Rearrangement of Sulfones.—The rearrangements were carried out in a three-neck, round-bottom flask equipped with a mechanical stirrer, gas inlet, pressure-equalizing dropping funnel, and a drying tube. The apparatus was flame dried and cooled by passing nitrogen through. The sulfone was dissolved in ether[15] and stirred in a nitrogen atmosphere, and an equivalent amount of commercial *n*-butyllithium in pentane (Foote Mineral Co., *ca.* 1.3 *M*) was added dropwise. The initially deep-red reaction mixture was stirred at room temperature for 4–6 hr in a nitrogen atmosphere. It was then poured into water and the layers were separated. Starting material was recovered by drying and evaporating the ether layer. The aqueous layer was acidified to pH 1 with concentrated HCl and extracted with ether. The ether extracts were combined and extracted with 0.5 *N* aqueous NaOH. The resulting basic solution was acidified to pH 1 and extracted with ether. The ether was dried ($MgSO_4$) decolorized, and evaporated giving the sulfinic acid products.

General Procedure for the Potassium *t*-Butoxide–Dimethyl Sulfoxide Induced Rearrangement of Sulfones.—The same dry apparatus was used as for the *n*-butyllithium-induced rearrangements. The potassium *t*-butoxide was dissolved in DMSO (previously dried over CaH_2), and to this well-stirred solution was added dropwise a solution of the sulfone in DMSO. The reaction mixture was stirred at room temperature for 6–18 hr, poured into water, and worked up in the same way as the *n*-butyllithium reactions except that ether extracts were washed several times with water to remove DMSO.

General Procedure for the Preparation of 2-Hydroxy-3,5-dichlorobenzyl Derivatives of Sulfinic Acids.[3]—The sulfinic acid was dissolved in a minimum amount of methanol, and the solu-

(13) V. N. Drozd and L. A. Nikonova, *Zh. Org. Khim.*, **4**, 1060 (1968).

(14) Microanalyses were determined by Dr. C. S. Yeh. Melting points and boiling points are uncorrected. Nmr spectra were taken on a Varian A-60 spectrometer using TMS as an internal standard.

(15) Mallinckrodt anhydrous ether was used after further drying over sodium.

tion was neutralized to a phenolphthalein end point with 1 *N* methanolic NaOH. An equimolar amount of 2-hydroxy-3,5-dichlorobenzyl chloride[16] in a minimum of methanol was added to the sulfinate solution. After standing overnight the crystalline sulfone was filtered and recrystallized from ethanol or ethyl acetate.

Rearrangement of Mesityl 1-Naphthyl Sulfone with *n*-Butyllithium in Ether.—The sulfone (1.55 g, 0.005 mol), on treatment with a 10% excess of *n*-butyllithium in hexane, rearranged to a sulfinic acid in 44% yield (0.68 g, yellow semisolid). The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared: mp 203–207° [lit.[3] mp 207–209° for 2-(1′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid, 175.5–177° for 2′-naphthylmethyl compound], mmp [with derivative from 2-(1′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid] 204–207°. The ir spectra of the 1′ and the 2′ derivatives were virtually identical except for the region 12–13 μ, in which the 1′-naphthyl compound showed peaks at 12.47, 12.57, and 12.72 μ, while the 2′-naphthyl compound showed peaks at 12.20 and 12.90 μ. The derivative prepared above had an ir identical with that of the 1′-naphthyl, but different from that of the 2′-naphthyl compound.

***m*-Toluenesulfonyl Chloride.**—The method of Zincke and Frohneberg was used.[17] *m*-Thiocresol (Aldrich, 59 g, 0.476 mol) was dissolved in 285 ml of glacial acetic acid, and chlorine was bubbled into the stirred solution for 4.5 hr. The solution initially darkened and then changed to a light yellow during the course of the reaction. After the reaction was complete, the solvent was evaporated at 50° under reduced pressure, and the residue was diluted with ether and washed with water. The ether solution was then washed with a $NaHCO_3$ solution until the wash was basic and then again with water and saturated NaCl. The resulting ether solution was dried over $MgSO_4$ and decolorized, and the ether was evaporated. The residue was vacuum distilled giving 83.78 g (92.5%) of a slightly yellow liquid: bp 88–90° (0.4 mm); ir (neat) 7.23 and 8.50 μ.

***o*-Toluenesulfonyl Chloride.**—The same procedure was used as that for the preparation of *m*-toluenesulfonyl chloride. When 116.55 g (0.94 mol) of *o*-thiocresol (Consol) in 500 ml of glacial acetic acid was used, and chlorine was passed into the solution for 4.5 hr, a 70% yield (124.7 g) of the sulfonyl chloride was obtained: bp 88–92° (1.5 mm); ir (neat) 7.25 and 8.42 μ.

Mesityl *m*-Tolyl Sulfone.—In a 1-l. three-neck flask were mixed 140.94 g (0.74 mol) of *m*-toluenesulfonyl chloride, 96 g (0.80 mol) of mesitylene, and 400 ml of carbon disulfide. To this well-stirred solution was slowly added 107 g (0.80 mol) of $AlCl_3$. The reaction was stirred at reflux for 20 hr. The solvent was then evaporated, the residue poured into 400 ml of ice-cold 3 *N* HCl, and the flask rinsed with HCl and ether. The aqueous acidic mixture was boiled for 1.5 hr to remove excess mesitylene and ether, cooled, and filtered, and the precipitate was washed with water. On recrystallization from 95% ethanol, 151.40 g (75%) of mesityl *m*-tolyl sulfone was obtained. After two more recrystallizations from ethanol an analytical sample was obtained: mp 101–103°; ir (Nujol mull) 7.60 and 8.68 μ; nmr ($CDCl_3$) δ 2.26 (s, 3 H), 2.35 (s, 3 H), 2.58 (s, 6 H), 6.93 (s, 2 H), and 7.2–7.7 (m, 4 H).

Anal. Calcd for $C_{16}H_{18}SO_2$: C, 70.04; H, 6.61; S, 11.69; mol wt, 274.4. Found: C, 70.23; H, 6.62; S, 11.70; mol wt, 274.6.

Mesityl *o*-Tolyl Sulfone.—The same procedure was used as that for the preparation of mesityl *m*-tolyl sulfone. When 124.7 g (0.654 mol) of *o*-toluenesulfonyl chloride and 80 g (0.667 mol) of mesitylene in 350 ml of CS_2 were treated with 93.2 g (0.70 mol) of $AlCl_3$, 131.88 g (73.6%) of mesityl *o*-tolyl sulfone was obtained after one recrystallization from ethanol. Decolorization with Darco followed by several more recrystallizations gave an analytical sample: mp 133–135°; ir (Nujol mull) 7.65 and 8.65 μ; nmr ($CDCl_3$) δ 2.27 and 2.30 (two unresolved singlets, 6 H), 2.47 (s, 6 H), 6.92 (s, 2 H), and 7.0–8.1 (m, 4 H).

Anal. Calcd for $C_{16}H_{18}SO_2$: C, 70.04; H, 6.61; S, 11.69; mol wt, 274.4. Found: C, 70.25; H, 6.52; S, 11.53; mol wt, 280.5.

Rearrangement of Mesityl *p*-Tolyl Sulfone with Potassium *t*-Butoxide in DMSO.—Mesityl *p*-tolyl sulfone (2.82, g 0.01 mol) in 60 ml of DMSO was treated with 1.5 g (0.014 mol) of potassium *t*-butoxide in 75 ml of DMSO for 6.5 hr. Pouring of the deep green reaction mixture into ice–water followed by work-up gave 0.91 g (32%) of recovered mesityl *p*-tolyl sulfone plus 1.53 g (54.3%) of sulfinic acid product as a white solid. The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared and shown by ir, melting point, and mixture melting point to be identical with that obtained from the *n*-butyllithium-induced rearrangement of mesityl *p*-tolyl sulfone.

Treatment of 6 with Potassium *t*-Butoxide in DMSO.—The cyclized product 6 (1.41 g, 0.005 mol), prepared by the method of Drozd,[5] was rearranged by the same procedure as that used for the rearrangement of mesityl *p*-tolyl sulfone. Treatment with 0.75 g (0.007 mol) of potassium *t*-butoxide in 75 ml of DMSO for 7.5 hr gave 0.90 g (63.8%) of crude acidic product as an off-white solid. The 2-hydroxy-3,5-dichlorobenzyl derivative had mp 140–141.5° (EtOH). Mixture melting point with the derivative from authentic 2-(4′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid showed no depression.

Rearrangement of Mesityl *m*-Tolyl Sulfone with *n*-Butyllithium.[7]—When the *meta* sulfone (2.08 g, 0.0076 mol) in 40 ml of ether was treated with 5.9 ml (0.0076 mol) of *n*-butyllithium in pentane diluted with 7.7 ml of ether, the initially deep red solution changed to a bright orange within *ca.* 2 min and slowly faded. After 4 hr at room temperature the turbid reaction mixture was almost colorless. On pouring into water and working up, the reaction gave 1.72 g (83.7%) of the unstable sulfinic acid 7: ir (neat) 3.1–3.7, 3.9 (broad), 9.2 (broad), and 9.5 μ; nmr ($CDCl_3$, impure compound with very poor integration) δ 2.17 and 2.20 (two unresolved singlets), 2.63 (s), 4.26 (s), 6.6–7.2 (m), and 7.87 (broad singlet).

The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared in 72.6% yield: mp 198.5–200.5° (EtOH); ir (Nujol mull) 2.97, 7.60, 7.75, 8.50, and 8.70 μ; nmr ($CDCl_3$) δ 2.25 (s, 6 H), 2.56 (s, 3 H), 3.6 (very broad peak, *ca.* 1 H), 4.27 (s, 2 H), 4.45 (s, 2 H), 6.8–7.2 (m, 7 H), and 7.44 (d, J = 2 cps, 1 H).

Anal. Calcd for $C_{23}H_{22}Cl_2SO_3$: C, 61.45; H, 4.94; Cl, 15.38; S, 7.12; mol wt, 449. Found: C, 61.25; H, 4.92; Cl, 15.66; S, 7.35; mol wt, 447.

Desulfination of the Sulfinic Acid, 7.—The lithium salt (3.68 g, 0.0131 mol) of the sulfinic acid was dissolved in 40 ml of boiling water, and 3.6 g (0.0132 mol) of $HgCl_2$ in 12 ml of hot water was added. The cloudy mixture was stirred and boiled for 20 min after which it was cooled, and the water was decanted off. The residue was washed with water and then stirred with 20 ml of ethanol and 20 ml of concentrated HCl with boiling for 1.5 hr. After cooling, acetone was added to the reaction mixture to precipitate inorganic products which were filtered off. The filtrate was evaporated on a hot plate giving a dark oil and tar which was distilled giving *ca.* 1 ml of clear liquid, bp 113–118° (0.5 mm), $n^{27}D$ 1.5614 [lit.[3] bp 114–120° (0.17 mm), $n^{27}D$ 1.5689]. The ir matched perfectly an authentic sample of 3,3′,5-trimethyldiphenylmethane, but was different from the ir of 3,4′,5-trimethyldiphenylmethane.[3] The nmr was identical with the published spectrum:[3] nmr ($CDCl_3$) δ 2.27 and 2.31 (two unresolved singlets, 6 H), 3.87 (s, 2 H), 6.84 (s, 3 H), and 7.0–7.2 (m, 4 H).

Rearrangement of Mesityl *m*-Tolyl Sulfone with Potassium *t*-Butoxide in DMSO.—Mesityl *m*-tolyl sulfone (2.82 g, 0.01 mol) in 60 ml of DMSO was treated with 1.5 g (0.014 mol) of potassium *t*-butoxide in 75 ml of DMSO for 6 hr. Work-up gave 0.34 g (12.1%) of recovered mesityl *m*-tolyl sulfone plus 2.31 g (82%) of acidic product as a clear tar. The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared in 62% yield: mp 200–202.5°; mmp (with derivative from *n*-butyllithium-induced rearrangement of mesityl *m*-tolyl sulfone) 201–203°; ir identical with *n*-butyllithium product.

1,5,7-Trimethyl-4a,9a-dihydrothioxanthene 10,10-Dioxide (8).[7]—Mesityl *m*-tolyl sulfone (2.7 g, 0.01 mol) was dissolved in 60 ml of ether, and 7.7 ml (0.01 mol) of *n*-butyllithium in pentane was added as rapidly as possible. After 1 min the deep-red reaction mixture was carefully poured onto crushed CO_2, and the pasty mixture was allowed to warm to room temperature. H_2SO_4 (10%) was then added and the two clear layers were separated. The organic layer was extracted with 10% KOH and the resulting basic solution was allowed to stand 16 hr while the product precipitated. The product was then filtered off and washed with water giving 0.75 g (27.8%) of 8 as a white solid: mp 176–180° (MeOH) (lit.[7] mp 179.5–180.5°); ir (Nujol mull) 6.03, 6.22, 6.35, 7.73, 8.68, and 8.80 μ; nmr ($CDCl_3$) δ 1.83 (s with fine splitting, 3 H), 2.25 (s, 3 H), 2.65 (s, 3 H), 2.9–4.2 (very broad multiplet, 4 H), 5.7–6.2 (m, 3 H), and 6.92 (s, 2 H).

(16) C. A. Buehler, *et al.*, *J. Org. Chem.*, **6**, 902 (1941).
(17) T. Zincke and W. Frohneberg, *Ber.*, **43**, 840 (1910).

1,5,7-Trimethylthioxanthene 10,10-Dioxide (9) from 8.[7]**—8** (1.37 g, 0.005 mol) was dissolved in 20 ml of $CHCl_3$, and 0.76 g (0.00475 mol) of bromine in 20 ml of $CHCl_3$ was added. The reaction mixture was stirred for 30 min after which the solvent was evaporated. The residue was heated at reflux with 20 ml of triethylamine for 6.25 hr. After evaporation of the solvent, the residue was stirred with benzene, filtered, and washed with benzene. The filtrate was dried ($MgSO_4$) and evaporated giving 1.2 g (88.3%) of a yellow solid which, after recrystallization from methanol, cyclohexane, and methanol again, gave a white solid: mp 167.5–169.5° (lit.[7] mp 167–167.5°); nmr ($CDCl_3$) δ 2.27 (s, 3 H), 2.35 (s, 3 H), 2.74 (s, 3 H), 4.07 (s, 2 H), 6.9–7.4 (m, 4 H), and 7.90 (t, J = 4.5 cps, 1 H).

Reaction of 8 with Potassium *t*-Butoxide in DMSO.—The same procedure was used as for the rearrangement of the mesityl tolyl sulfones. A 5.5-hr reaction time gave 9% of recovered starting material plus 75% of sulfinic acid product as an oil. The 2-hydroxy-3,5-dichlorobenzyl derivative had mp 197–201.5°; mmp [with derivative from authentic 2-(3′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid] 198–202°; ir of derivatives identical.

Reaction of 8 with *n*-Butyllithium in Ether.—The same procedure was used as for the rearrangment of the mesityl tolyl sulfones. When 0.005 mol of **8** was treated with 0.005 mol of *n*-butyllithium in 40 ml of ether, a quantitative yield of crude acid was obtained. The 2-hydroxy-3,5-dichlorobenzyl derivative had mp 198–201°, mmp 198–201°.

Preparation of 10 from 8 with Sodium Ethoxide in Ethanol.—Soldium ethoxide was prepared by dissolving 2 g (0.087 g-atom) of Na in 40 ml of EtOH. This solution was slowly added to a suspension of 1.58 g (0.0029 mol) of the sulfone **8** in 20 ml of EtOH in a nitrogen atmosphere. The reaction mixture became homogeneous on heating to reflux, and stirring was continued at reflux for 20 hr. The reaction mixture was then poured into 100 ml of water and worked up in the same way as in the *n*-butyllithium-induced rearrangements giving 0.76 g (48%) of an acidic product. The nmr of the sulfinic acid was different from that obtained by butyllithium-induced rearrangement of mesityl *p*-tolyl or *m*-tolyl sulfone: nmr ($CDCl_3$) δ 2.19 (s with very fine splitting, 6 H), 2.63 (s, 3 H), 4.34 (s, 2 H), 6.8–7.3 (m, 6 H), and 8.87 (s, 1 H).

The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared in 37% yield and had mp 168–172°, which was also greatly different from the two isomeric sulfinic acid derivatives. It was therefore assumed, in analogy to the reaction of **6** with sodium ethoxide, that the sulfinic acid had the structure of 2-(2′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid: derivative ir (Nujol mull) 2.89, 7.6, 7.75, and 8.7μ; nmr ($CDCl_3$) δ 2.24 (s, 6 H), 2.60 (s, 3 H), 4.17 (s, 2 H), 4.32 (s, 2 H), 5.86 (broad s, 1 H), and 6.7–7.3 (m, 8 H).

Rearrangement of Mesityl *o*-Tolyl Sulfone with *n*-Butyllithium.—When 2.7 g (0.01 mol) of mesityl *o*-tolyl sulfone in 90 ml of ether was treated with 7.7 ml of butyllithium in pentane (0.01 mol) diluted with 10 ml of ether, the initially deep-red reaction mixture slowly lightened to an orange. After 5.5 hr at room temperature followed by pouring into water and working up, 1.92 g (71%) of acidic product, **10**, was obtained as a white solid, which darkened only slightly on standing 6 weeks: mp 86–87° dec. The nmr and ir were identical with the spectra of the product produced from the ethoxide induced rearrangement of **8**.

The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared in 66% yield: mp 169.5–171.5°; ir and nmr spectra identical with those from the derivative prepared from the ethoxide product. Mixture melting point showed no depression.

Anal. Calcd for $C_{23}H_{22}Cl_2SO_3$: C, 61.45; H, 4.94; Cl, 15.38; S, 7.12; mol wt, 449. Found: C, 61.38; H, 4.91; Cl, 15.65; S, 7.08; mol wt, 457.

Rearrangement of Mesityl *o*-Tolyl Sulfone with Potassium *t*-Butoxide in DMSO.—When 2.5 g (0.0089 mol) of mesityl *o*-tolyl sulfone in 60 ml of DMSO was treated with 1.5 g (0.014 mol) of *t*-BuOK in 75 ml of DMSO for 6 hr followed by work-up, 2.39 g (96%) of sulfinic acid product was obtained as a white solid. The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared in 50% yield: mp 170–172°; mmp [with derivative from authentic 2-(2′-methylbenzyl)-4,6-dimethylbenzenesulfinic acid] 169–172°.

1,5,7-Trimethylthioxanthene 10,10-Dioxide (9) from 10.—**10** (41.33 g, 0.151 mol) was dissolved in 30% NaOH and neutralized with concentrated HCl until just basic to phenolphthalein (*ca.* 150-ml total volume). Cl_2 was then bubbled into the stirred solution for 4 hr after which the turbid reaction mixture was extracted with benzene and ether, and the organic extract was dried, decolorized, and evaporated giving 38.04 g of a yellow tar. This tar was dissolved in 200 ml of CH_2Cl_2, and 20.10 g (0.151 mol) of $AlCl_3$ suspended in 250 ml of CH_2Cl_2 was slowly added. The reaction mixture was stirred for 16 hr at room temperature. It was then poured into an ice–concentrated HCl mixture, and the organic layer was separated and washed with 6 *N* HCl, water, and saturated NaCl, dried over $MgSO_4$, and evaporated giving 21.33 g of a thick red tar. The red tar was stirred with ethanol at room temperature, filtered, and washed with ethanol giving 1.14 g (2.76%) of a brown solid. Concentration of the filtrate followed by cooling in an ice bath led to several more crops of off-white crystals giving a total of 4.93 g (12%) of the product which was identical with the product from bromination–dehydrohalogenation of **8**.

Preparation of 2,4,9a-Trimethyl-4a,9a-dihydrothioxanthene 10,10-Dioxide (12). A. Protonation Work-Up.—Mesityl *o*-tolyl sulfone (6.8 g, 0.025 mol) in 250 of ether was cooled in an ice bath. To this well-stirred solution was rapidly added 19.1 ml (0.025 mol) of *n*-butyllithium in pentane, and the cold solution was stirred for 2.5 min. It was then rapidly poured into 200 ml of water and the layers were separated. The aqueous layer on work-up gave 2.43 g (35.8%) of sulfinic acid product, **10**. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated, giving 3.36 g (49.4%) of white solid which consisted of starting sulfone and product. Recrystallization from methanol gave very little separation. An nmr of the product mixture showed an approximate composition of 40% **12** to 60% starting sulfone, thus giving an actual yield of **12** of *ca.* 20%.

B. Carboxylation–Decarboxylation Work-Up.—A nonhomogenous mixture of 54 g (0.2 mol) of mesityl *o*-tolyl sulfone and 1900 ml of ether was rapidly stirred in an ice bath. To this was added as rapidly as possible 155 ml (1 equiv) of *n*-butyllithium in pentane. As soon as addition was complete, the deep-red reaction mixture was carefully poured onto 1 lb. of crushed CO_2. The slurry was stirred and allowed to warm to room temperature, after which 900 ml of 10% H_2SO_4 was added with stirring, and the layers were separated. The organic layer was then washed with water and extracted with a total of 1 l. of 10% KOH. Upon drying and evaporating the organic solution, 10.42 g (19.3%) of starting sulfone was recovered. The basic extract was left standing 6 days during which time the product precipitated giving, on filtration and washing with water, 2.18 g (4.04%) of a white crystalline solid: mp 157–158° (EtOH); ir (Nujol mull) 5.92, 7.72, and 8.95 μ; nmr ($CDCl_3$) δ 1.23 (s, 3 H), 1.55 (s, 3 H), 2.10 (s, 3 H), 2.90 and 3.27 (two incompletely resolved, distorted doublets, J = 14.5 cps, 2 H), 3.62 (s, 1 H), 4.84 (broad singlet, 1 H), 5.82 (broad singlet, 1 H), 7.1–7.6 (m, 3 H), and 7.7–8.0 (m, 1 H).

Anal. Calcd for $C_{16}H_{18}SO_2$: C, 70.04; H, 6.61; S, 11.69; mol wt, 274.4. Found: C, 70.19; H, 6.90; S, 11.83; mol wt, 271.6.

The basic filtrate was acidified with concentrated HCl and extracted with ether, the ether extracted with 0.5 *N* NaOH, and the resulting aqueous solution acidified and extracted with ether. The ether solution was dried, decolorized, and evaporated giving 41.33 g (76.6%) of impure sulfinic acid **10**.

Registry No.—*m*-Toluenesulfonyl chloride, 1899-93-0; *o*-toluenesulfonyl chloride, 133-59-5; mesityl *m*-tolyl sulfone, 21128-93-8; mesityl *o*-tolyl sulfone, 21991-14-0; **7**, 21991-15-1; **7** (2-hydroxy-3,5-dichlorobenzyl derivative), 24299-63-6; **8**, 24343-77-9; **9**, 21128-30-3; **10**, 21128-31-4; **12**, 21995-82-4.

Acknowledgment.—This investigation was supported by Public Health Service Grant No. CA-04536-11 from the National Cancer Institute and by the National Science Foundation Grant No. GP-05175.

Synthesis and Configurational Assignments of Diastereomeric β-Hydroxy Sulfones

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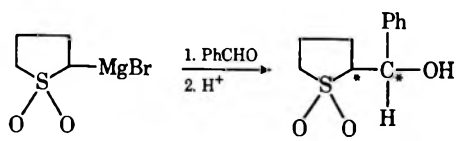
Reported here are the isolations of a number of diastereomeric β-hydroxy sulfones obtained by the condensations of α-sulfonyl carbanions with aldehydes. Configurations were assigned from nmr spectra of the resulting *threo* and *erythro* isomers. Sodium borohydride reductions of β-keto sulfones were found to produce the *threo* isomers in excellent yields. Conversion of *threo* **1** to the β-chloro sulfone by treatment with thionyl chloride proceeds with complete epimerization. Under identical conditions the *erythro* isomer **2** proceeds with complete retention of configuration. Preparation of the exocyclic *cis* olefin **15** was accomplished by dehydration and dehydrohalogenation of **2** and **10**, respectively. The less stable *trans* olefin **16** was prepared *via* the intramolecular cyclization of an acetylenic mercaptan.

While the preparations of α metalated sulfones and their reactions with carbonyl moieties to form β-hydroxy sulfones have been extensively investigated,[1] little of this work has been done with sulfones which can give rise to diastereomers. In cases where such sulfones have been used,[1a,b,d] determination of isomer ratios in the products, isolation of pure *erythro* and *threo*[2] isomers, and assignment of configuration to these isomers have either been ignored or circumvented by oxidation of the mixtures to the β-keto sulfones. It was therefore the purpose of this investigation to isolate pure diastereomeric β-hydroxy sulfones and assign configurations by spectral and chemical methods.

In 1954 the preparation of phenyl(1,1-dioxy-2-thiolanyl)carbinol from 2-thiolanylmagnesium bromide 1,1-dioxide and benzaldehyde was reported (no stereochemistry specified).[1b] As can be readily seen, two



(1)

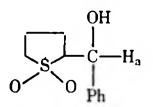
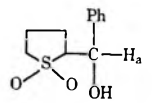
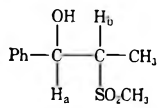
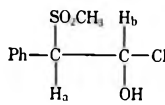
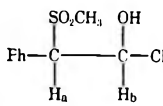
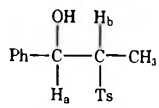
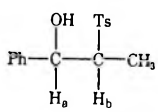
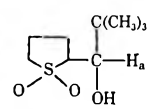
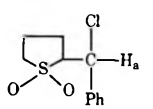
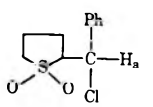
adjacent centers of asymmetry (*) are present which could result in *erythro* and *threo* diastereomers. Upon reinvestigation of this reaction we found that the product was indeed a 50:50 mixture of *threo* (**1**) and *erythro* (**2**) phenyl(1,1-dioxy-2-thiolanyl)carbinol.[3]

Configurational assignments were made on the basis of the magnitude of the coupling constants between the vicinal methinyl protons on the asymmetric centers (Table I). The vicinal coupling constant can be predicted from its relationship to the dihedral angle formed by H–C–C–H.[4] Similar assignment of stereochemistry by nuclear magnetic resonance spectroscopy has been reported for diastereomeric amino alcohols.[5-7]

The large difference in the magnitude of the vicinal coupling constants of the methinyl protons in **1** and **2** (see Table I) suggests preferred residence in different conformations. This requirement is best satisfied by the conformers shown in Chart I. Using theoretical calculations[4] one predicts dihedral angles of 171 and 56°

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA[a]

No.	Compound	Configuration	Chemical shift, δ, H_a	J_{ab}, Hz	Mp, °C
1		*threo*	5.03	9.0	159–159.5
2		*erythro*	5.46	2.2	97–98
3		*threo*	4.87	9.5	130–131
4		*threo*	4.08	9.0	153–154
5		*erythro*	3.97	2.5	114.5–115
6		*threo*	4.90	9.0	104–105
7		*erythro*	5.47	1.5	*b*
8		*erythro*	3.91	1.0	103.5–105
9		*threo*	5.06	10.5	193–194
10		*erythro*	5.22	9.0	159–160

[a] Determined on a Varian Model A-60 (60 MHz) spectrometer in $CDCl_3$ solution. [b] A pure sample, free of **6**, could not be obtained.

(1) (a) L. Field and J. W. McFarland, *J. Amer. Chem. Soc.*, **75**, 5582 (1953); (b) W. E. Truce and K. R. Buser, *ibid.*, **76**, 3577 (1954); (c) H. D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963); (d) D. F. Tavares and P. F. Vogt, *Can. J. Chem.*, **45**, 1519 (1967); (e) E. M. Kaiser and C. R. Hauser, *Tetrahedron Lett.*, 3341 (1967).

(2) The terms *erythro* and *threo* refer to *dl-erythro* and *dl-threo*, respectively.

(3) Isomer ratios were determined by nmr spectroscopy.

(4) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

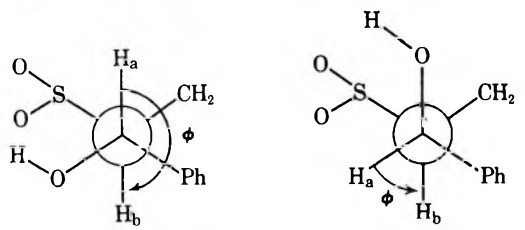
(5) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961).

(6) J. C. Randall, R. L. Vaulx, M. E. Hobbe, and C. R. Hauser, *J. Org. Chem.*, **30**, 2035 (1965).

(7) M. E. Munk, M. K. Meilahn, and P. Franklin, *ibid.*, **33**, 3480 (1968).

CHART I

PREFERRED CONFORMATIONS OF *threo*- AND *erythro*-PHENYL(1,1-DIOXY-2-THIOLANYL)CARBINOL

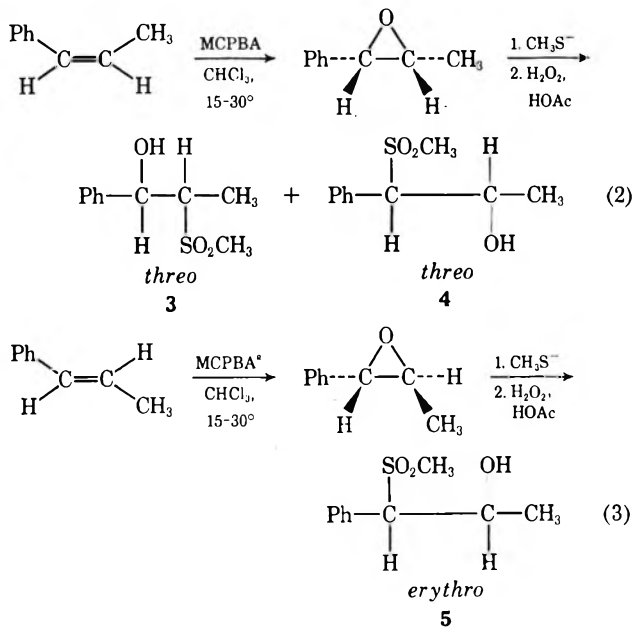


threo — J_{ab} = 9.0 Hz, ϕ_{calcd} = 171°

erythro — J_{ab} = 2.2 Hz, ϕ_{calcd} = 56°

from the coupling constants 9.0 and 2.2 Hz, respectively. On this basis we have assigned the *threo* configuration to the isomer with J_{ab} = 9.0 Hz. This isomer resides primarily in the *anti* conformation (Chart I). The *erythro* isomer resides chiefly in the *gauche* conformation and therefore has the coupling constant of 2.2 Hz. These values are in good agreement with those previously reported in similar conformational studies.[5-7]

In order to confirm these stereochemical assignments and test the generality of this method of assignment of stereochemistry in other β-hydroxy sulfones, it was deemed necessary to synthesize compounds of unambiguous configuration. This was accomplished using *cis*- and *trans*-propenylbenzene. These olefins

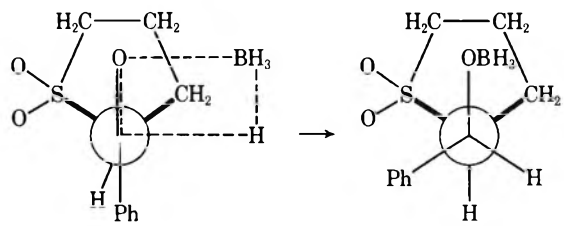


were converted to the corresponding *cis*- and *trans*-propenylbenzene oxides in near quantitative yields by treatment with *m*-chloroperoxybenzoic acid. Treatment of the *cis* epoxide with sodium methanethiolate in ethanol, followed by oxidation of the β-hydroxy sulfides with peracetic acid, produced a mixture of *threo*-2-methylsulfonyl-1-phenyl-1-propanol (**3**) and *threo*-1-methylsulfonyl-1-phenyl-2-propanol (**4**) (eq 2). Structural assignment of **3** was based on the mass spectrum in which the major ion fragment was *m/e* 107 which corresponds to cleavage of the molecule at the C_1–C_2 bond. The structures of **4** and **5** were established by oxidation of the alcohols to 1-phenyl-1-methylsulfonylacetone with the chromium trioxide–pyridine complex.[9] *erythro*-1-Methylsulfonyl-1-phenyl-2-propanol (**5**) was prepared in a similar fashion from the *trans* epoxide (eq 3). None of the *erythro* benzylic alcohol was isolated from this reaction.[10] The observed vicinal coupling constants of **3** and **4** were 9.5 and 9.0 Hz corresponding closely with that of **1**. A value of 2.5 Hz was observed for **5** which supports the configurational assignment of **2**.

In the course of our investigation it came to our attention that the synthesis and nmr spectrum of 1-phenyl-2-(*p*-tolylsulfonyl)-1-propanol had been recorded previously.[1d] These authors obtained a compound melting from 99 to 100°. A doublet at δ 1.5 with a coupling constant of 7.5 Hz was attributed to the benzylic methinyl proton. We wish to report that this assignment is in error. Treatment of ethyl *p*-tolyl sulfone with *n*-butyllithium in tetrahydrofuran followed by addition of benzaldehyde produced a 93% yield of a mixture composed of 62% *erythro*-1-phenyl-2-(*p*-tolylsulfonyl)-1-propanol (**7**) and 38% *threo* isomer (**6**). The methinyl resonance in question appears at δ 4.90 (J_{ab} = 9.0 Hz) for **6** and δ 5.47 (J_{ab} = 1.5 Hz) for **7** which corresponds closely with compounds previously discussed here. Apparently the authors were dealing with a mixture containing 75% **6** and 25% **7**. The resonance which was attributed to the methinyl proton is in reality due to the alkyl methyl grouping of **7**. The doublet at δ 1.17 corresponds to the methyl grouping of **6**.

Further evidence for the above stereochemical assignments was obtained through the sodium borohydride reduction of α-(*p*-tolylsulfonyl)propiophenone (**11**) and 2-thiolanyl phenyl ketone (**12**). Applying the rule of steric control of asymmetric induction[11] one would predict attack from the least hindered side of the conformer shown in Chart II and production of the

CHART II



threo alcohol. The other conformations of this molecule were ruled out on the basis of severe steric and electrostatic repulsions. Reduction of **12** with sodium borohydride in aqueous methanol produced a nearly quantitative yield of β-hydroxy sulfone. The product contained 95% *threo* isomer **1** and 5% *erythro* isomer **2**. Similarly, reduction of **11** resulted in a 97%

(8) *m*-Chloroperoxybenzoic acid.

(9) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

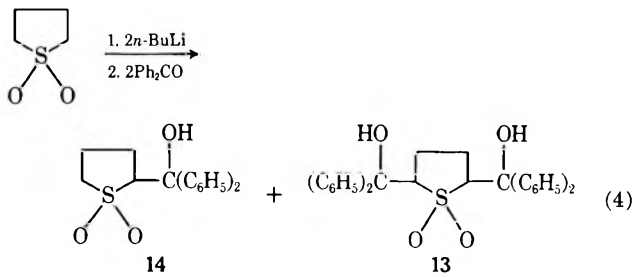
(10) The appearance of the "abnormal" ring opening leading to product **3** may be related to hindered rotation on the part of the phenyl ring in the *cis* epoxide. The resulting noncoplanarity of the phenyl group would hinder attack at the benzylic carbon atom sterically as well as through decreased resonance stabilization of the incipient positive charge in the transition state. Similar results were observed by H. Audier, *et al.*, *Bull. Soc. Chim. Fr.*, 2811 (1966).

(11) For leading references, see H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 28–33.

yield of **6** and 3% **7**. The high degree of stereospecificity indicates the importance of large steric factors present in these molecules.

The metalation of sulfones has been achieved with a wide variety of bases.[1] We have found *n*-butyllithium in THF to be an excellent base–solvent system for metalation and subsequent condensation with carbonyl moieties. Reaction times are short and yields are high. The condensation works well with aldehydes, ketones, and carboxylic acid esters and is not limited by side reactions such as are found with liquid ammonia.[1d] The ratios of diastereomers produced in eq 1 appear to be somewhat influenced by the cation associated with the carbanion although the effect is small, the greatest difference being observed with the *n*-butyllithium–tetramethylethylenediamine complex[12] (65 ± 2% **2** and 35 ± 2% **1**).

When the sulfone is capable of forming an α,α' dicarbanion (*i.e.*, sulfolane), care must be exercised to add the *n*-butyllithium slowly in a dropwise fashion or appreciable quantities of diaddition products may result.



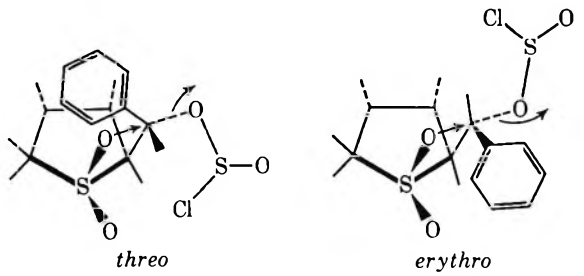
(4)

Treatment of sulfolane with 2 equiv of *n*-butyllithium in THF followed by 2 equiv of benzophenone afforded an 80% yield of diadduct **13** and 18% monoadduct **14**. Hauser[1e] has reported that treatment of sulfolane with 2 mol of lithium amide followed by benzophenone produced only monoadduct, while use of sodium amide resulted in a 41% yield of **13** and a 48% yield of **14**. Apparently *n*-butyllithium in THF is a superior system for such 1,3 dicarbanions.

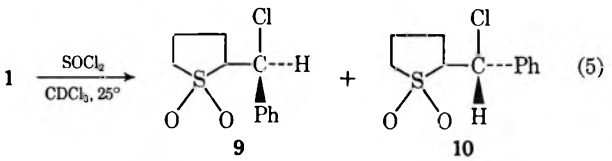
While attempting to assign stereochemical configurations to **1** and **2** we converted them to the *threo* (**9**) and *erythro* (**10**) chlorides with thionyl chloride (eq 5). Treatment of **1** with thionyl chloride in deuteriochloroform resulted in the quantitative conversion to a 1:1 mixture of **9** and **10** in 12 hr. Treatment of **2** under the same conditions provided a quantitative yield of **10** in 72 hr. Use of various solvents (dioxane, thionyl chloride, and pyridine), as well as lower temperatures, had no effect on the products formed. The *threo* isomer always proceeded with epimerization while the *erythro* isomer always proceeded with retention of configuration. These results are perhaps best explained by participation of the sulfonyl oxygens in back-side protection of the incipient carbonium ion (Chart III). This would prevent back-side attack and therefore result in retention of configuration. This conformation is considered the most stable owing to minimal steric interaction. In order for back-side assistance to occur in the *threo* isomer, the molecule must assume a conformation in which the aromatic nucleus is seated directly upon the sulfolane ring. This produces severe steric interaction as well as interfering with the ability

(12) D. J. Peterson, *J. Org. Chem.*, **32**, 1717 (1967).

CHART III

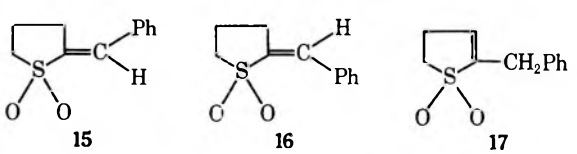


of the aromatic nucleus to attain coplanarity with the incipient carbonium ion thereby interfering with resonance stabilization. Such participation by neighboring groups has been studied for the decomposition of β-phenyl chlorosulfites.[13]



(5)

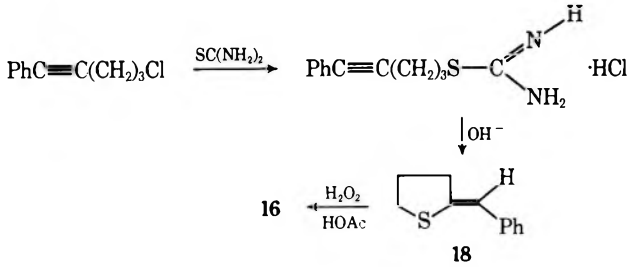
Further support for these configurational assignments was obtained from the results of base-catalyzed dehydrohalogenation of **9** and **10**. On the basis of earlier observations of bimolecular eliminations of diastereomeric halides,[14] the preferred *trans* elimination of **10** should lead to formation of the *cis* olefin (**15**) as the predominant product. By similar considerations, **9** should be transformed primarily into the *trans* olefin (**16**). These systems are, however, directly analogous to the diastereomeric 2-*p*-tolylsulfonyl-1,2-diphenyl-1-chloroethanes studied by Cristol[15] in which dehydrohalogenation resulted in stereoconvergent eliminations and production of the *cis* olefin from both the *erythro* and *threo* isomers. Similar steric interactions between the sulfonyl and aryl groupings in the transition state should lead to formation of **15** from **9** *via cis* elimination. The rate of elimination should be considerably slower for **9** than for **10** in which a *trans* elimination occurs. Treatment of **10** with triethylamine in chloroform at 25° gave essentially quantitative conversion to **15** in 48 hr. Under the same conditions **9** showed no detectable elimination even after 2 weeks. Attempted dehydrohalogenation of **9** with triethylamine in refluxing benzene for 24 hr again resulted in quantitative recovery of starting material. Treatment of **9** and **10** with potassium *t*-butoxide in benzene gave dehydrohalogenation; however, the olefinic products were isomerized to the endocyclic olefin (**17**). Attempted isomerization of **16** to **15** in refluxing ethanolic sodium hydroxide also produced **17** as the major product.



The synthesis of **16** was accomplished by the sequence shown in Scheme I. 5-Chloro-1-phenyl-1-pentyne was converted to the corresponding thiouronium salt by reaction with thiourea. Subsequent treatment with

(13) D. J. Cram, *J. Amer. Chem. Soc.*, **75**, 332 (1953).
(14) J. F. Bunnett, *Angew. Chem., Int. Ed. Engl.*, **1**, 225 (1962).
(15) S. J. Cristol and P. Pappas, *J. Org. Chem.*, **28**, 2066 (1963).

SCHEME I



hydroxide resulted in the expected *trans* sulfide (**18**) *via* intramolecular *trans* addition to the acetylenic linkage. Such additions in intermolecular thiolate additions have been extensively studied.[16] Oxidation of **18** with peracetic acid afforded **16** in excellent yields.

Other behavioral differences between *erythro*- and *threo*-hydroxy sulfones were observed upon acid-catalyzed dehydration of **1** and **2**. **2** was converted to **15** in high yield in refluxing 85% phosphoric acid in 1 hr. The *threo* isomer **1** was recovered intact after 1 hr under the same conditions. When treated for 24 hr at reflux, **1** gave extensive decomposition, and the only product isolated was apparently a salt melting above 300°. The *erythro* alcohols and chlorides studied here generally had lower melting points and higher degrees of solubility in organic solvents such as chloroform and benzene than the corresponding *threo* isomers.

Experimental Section[17]

Reagents.—*n*-Butyllithium in hexane was purchased from Foote Mineral Corp. and Alfa Inorganics. Sulfolane was obtained from Eastman Organic Chemicals. Reagent grade THF was distilled from lithium aluminum hydride prior to use. *m*-Chloroperoxybenzoic acid (85%) was purchased from Aldrich Chemical Co.

Phenyl(1,1-dioxy-2-thiolanyl)carbinol. A.—*n*-Butyllithium (0.05 mol) in hexane under a nitrogen atmosphere was cooled below 20°, and 5.8 g (0.05 mol) of TMEDA was added slowly, followed by 6 g (0.05 mol) of sulfolane in 10 ml of THF; stirring was continued for 1 hr. The solution was cooled to −30° and 6.36 g (0.06 mol) benzaldehyde was added and stirring was continued for 1 hr. The mixture was acidified with aqueous NH_4Cl, and the organic phase was separated and dried over Na_2SO_4. Filtration and removal of solvent *in vacuo* gave 10 g of a viscous oil that was shown by nmr to contain 65% *erythro* isomer **2** and 35% *threo* isomer **1**. The oil was dissolved in benzene–hexane and 9.6 g (85%) of a white solid precipitated, mp 80–82°. A second recrystallization raised the melting point to 87–88°. This mixture was submitted for analysis.

Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24; S, 14.17. Found: C, 58.47; H, 6.48; S, 13.96.

Subsequent recrystallization from benzene, benzene–hexane, and benzene–CCl_4 yielded **2** [mp 97–98°; nmr ($CDCl_3$) δ 1.68–2.56 (m, 4, $-CH_2CH_2-$), 2.90–3.50 (m, 4, CH_2SO_2CH and OH), 5.46 (d, 1, $-C(H)(OH)C_6H_5$), and 7.35 (s, 5, aromatic H)] and **1** [mp 159–159.5° (lit.[1b] 159–159.5°); nmr ($CDCl_3$) δ 1.55–2.35 (m, 4, $-CH_2CH_2-$), 2.95–3.50 (m, 3, CH_2SO_2CH), 3.56 (s, 1, OH), 5.03 (d, 1, $-C(H)(OH)C_6H_5$), and 7.47 (s, 5, aromatic H)].

B.—Synthesis was carried out as previously described by Truce and Buser[1b] with the exception that an equimolar amount of benzaldehyde was used. A yield of 20% of a mixture composed of 50% **1** and 50% **2** was obtained.

C.—Sulfolane (18 g, 0.15 mol) in 200 ml of THF under nitrogen was cooled to −30°, and *n*-butyllithium (0.15 mol) in hexane was added dropwise. After 1 hr benzaldehyde (15.9 g, 0.15 mol) in 100 ml of THF was added, and stirring was continued for 3 hr. Work-up as in A produced 26.8 g (79%) of a mixture of 43% **2** and 57% **1**.

trans-**Propenylbenzene Oxide.**—*trans*-Propenylbenzene (11.8 g, 0.1 mol) in 100 ml of $CHCl_3$ was cooled to 15°, and a solution of 85% *m*-chloroperoxybenzoic acid (25 g) in 300 ml of $CHCl_3$ was added dropwise maintaining the temperature below 30°. After stirring 1 hr at room temperature the excess peracid was decomposed with 10% aqueous Na_2SO_3. The organic layer was washed with 10% Na_2CO_3 until basic and then H_2O until neutral. After drying over Na_2SO_4, filtration, and removal of solvent, 12.8 g (95.6%) of the epoxide was obtained: nmr ($CDCl_3$) δ 1.33 (d, 3, CH_3), 2.90 (m, 1, $HCCH_3$), 3.47 (d, 1, HCC_6H_5), 7.20 (s, 5, C_6H_5).

cis-**Propenylbenzene Oxide.**—The *cis* epoxide was prepared from *cis*-propenylbenzene[18] and MCPBA in the same manner as the *trans* isomer in 94% yield: nmr $CDCl_3$, δ 1.00 (d, 3, CH_3), 3.20 (m, 1, $HCCH_3$), 3.95 (d, 1, HCC_6H_5), 7.21 (s, 5, C_6H_5).

threo-**1-Phenyl-2-(methylsulfonyl)-1-propanol (3) and** *threo*-**2-Phenyl-1-(methylsulfonyl)-2-propanol (4).**—To a solution of Na (0.80 g) in 50 ml of ethanol was added 3 ml of methanethiol. After stirring 15 min, 2.6 g (19.4 mmol) *cis*-propenylbenzene oxide was added, and stirring was continued for 2 hr at 35°. After acidification with 10% HCl and extraction with CH_2Cl_2, removal of solvent gave the crude β-hydroxy sulfide. This was dissolved in 20 ml of HOAc, and 15 ml of 30% H_2O_2 was added. The solution was heated at 83° for 2 hr and poured onto ice. The solution was extracted with $CHCl_3$, neutralized with 10% Na_2CO_3, and dried; solvent was removed *in vacuo* to yield 3.1 g (75%) of a white solid, mp 110–130° (31% isomer **3** and 69% isomer **4**). This was dissolved in hot benzene, and 1.6 g of a 1:1 mixture of **3** and **4** precipitated on cooling. Hexane was added to the mother liquor and 200 mg of **3** was obtained: mp 130–131; nmr ($CDCl_3$) δ 1.00 (d, 3, $HCCH_3$), 3.02 (s, 3, SO_2CH_3), 3.18–3.80 (m, 2, OH and $HCCH_3$), 4.87 (d, 1, HCC_6H_5), 7.32 (s, 5, C_6H_5); mass spectrum (70 eV) *m/e* (relative intensity) 214 (2.4), 213 (25.8), 196 (1.7), 107 (100). The 1:1 mixture was recrystallized several times from benzene to obtain **4**: mp 153–154°; nmr ($CDCl_3$) δ 1.08 (d, 3, $HCCH_3$), 2.81 (s, 3, SO_2CH_3), 3.50–3.70 (m, 1, OH), 4.08 (d, 1, SO_2CH), 4.65–5.00 (m, 1, $HCCH_3$), 7.38 (s, 5, C_6H_5).

erythro-**1-Phenyl-1-(methylsulfonyl)-2-propanol (5).**—Sodium (1.2 g) was dissolved in 50 ml of ethanol, and methanethiol (3.0 g, 63 mmol) was added. After stirring 10 min, *trans*-propenylbenzene oxide (5 g, 37.3 mmol) in 20 ml of ethanol was added, and stirring was continued for 2 hr at room temperature (32°). Work-up as with **3** and **4** gave the crude sulfide. This was heated at 85° for 2 hr in a solution of 25 ml of HOAc and 20 ml of 30% H_2O_2. Treatment as above and recrystallization from 95% ethanol gave 5.0 g (58%) of white crystals: mp 114.5–115°; nmr (CCl_3) δ 1.20 (d, 3, $HCCH_3$), 2.68 (s, 3, SO_2CH_3), 3.07 (d, 1, OH), 3.97 (d, 1, $HCSO_2CH_3$), 4.78–5.20 (m, 1, $HCCH_3$), 7.25–7.80 (m, 4, C_6H_5).

Anal. Calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.59; S, 14.96. Found: C, 56.06; H, 6.67; S, 14.74.

1,1-Dioxy-2-thiolanyl Phenyl Ketone (12).—A solution of sulfolane (12 g, 0.1 mol) in 200 ml of THF under nitrogen was cooled to −68° and *n*-butyllithium in hexane (0.1 mol) was added dropwise with stirring. After 1 hr ethyl benzoate (16 g, 0.107 mol) was added rapidly and stirred 15 min. The solution was acidified with 10% HCl. The organic phase was extracted with 10% NaOH. Cooling of the basic layers and acidification with HCl gave an oil which crystallized on standing. This was recrystallized from 95% ethanol to obtain 9.4 g (42%) of **12**: mp 91–93°; nmr ($CDCl_3$) δ 1.80–2.80 (m, 4, CH_2CH_2), 2.9–3.0 (t, 2, CH_2SO_2), 4.87 (t, 1, $SO_2C(H)(CO)$), 7.20–7.70 (m, 3, aromatic H), and 7.70–8.20 (m, 2, aromatic H).

Reduction of 12.—A solution of **12** (1 g, 4.45 mmol) in 50 ml of methanol was cooled to 15° and $NaBH_4$ (0.8 g) in 10 ml of H_2O was added dropwise keeping the temperature at 10–15°. After 5 hr the reaction was acidified with 15 ml of 10% HCl, and the product was extracted with $CHCl_3$. Removal of solvent produced 0.98 g of a mixture of 95% **1** and 5% **2**, mp 153–155°. Two recrystallizations from benzene–hexane gave 0.93 g (93%) of **1**, mp 159–159.5°.

(16) (a) W. E. Truce and R. F. Heine, *J. Amer. Chem. Soc.*, **79**, 5311 (1957); (b) W. E. Truce, H. G. Klein, and R. B. Kruse, *ibid.*, **83**, 4636 (1961).

(17) All melting points are uncorrected. The nmr spectra were obtained using a Varian A-60 spectrophotometer. Mass spectral data were obtained on a CEC 21110-B spectrometer. Microanalyses were performed by Dr. C. S. Yeh and staff.

(18) The authors wish to express their appreciation to Dr. W. Chaisson for the preparation of the *cis*-propenylbenzene used in this work.

1-Phenyl-2-(*p*-tolylsulfonyl)-1-propanol (6 and 7).—A solution of *p*-tolyl ethyl sulfone (3.7 g, 0.02 mol) in 100 ml of THF under nitrogen was cooled to −28°, and *n*-butyllithium (0.02 mol) in hexane was added with stirring. After 5 min benzaldehyde (2.0 g, 0.019 mol) was added and stirring was continued 15 min. Work-up as above gave 5.3 g (93%) of a mixture of the *erythro* isomer **7** (62%) and the *threo* isomer **6** (38%). Attempts to separate the isomers were unsuccessful. The nmr for **7** was obtained by subtraction of the nmr of **6** from the above mixture: nmr ($CDCl_3$) δ 1.18 (d, 3, $HCCH_3$), 2.42 (s, 3, $CH_3C_6H_4$), 3.10–3.70 (m, 1, $SO_2C(H)(CH_3)$), 4.50 (s, 1, OH), 5.47 (d, 1, HCC_6H_5), 7.20–7.9 (m, 9, aromatic H).

2-(*p*-Tolylsulfonyl)propiophenone (11).—Ethyl *p*-tolyl sulfone (2.0 g) in 40 ml of THF was cooled to −30° under nitrogen, and an equivalent amount of *n*-butyllithium in hexane was added. After 5 min ethyl benzoate (3.0 g) was added and stirring was continued 7 min. Acidification with 10% HCl and subsequent work-up gave 1.6 g of **11**: mp 98.5–99.5° (lit.[1a] 99.5–100.5°); nmr ($CDCl_3$) δ 1.56 (d, 3, $HCCH_3$), 2.40 (s, 3, $CH_3C_6H_4$), 5.18 (q, 1, $HCCH_3$), 7.1–8.1 (m, 9, aromatic H).

***threo*-1-Phenyl-2-(*p*-tolylsulfonyl)-1-propanol (6).**—To a solution of **11** (1 g, 3.52 mmol) in 50 ml of methanol at 15° was added $NaBH_4$ (0.8 g) in 10 ml of H_2O with 3 drops of 10% NaOH. The solution was stirred at 10° for 1.5 hr and at room temperature for 3.5 hr. Work-up with 10% HCl gave 1 g (100%) of white crystals which was a mixture of 97% **6** and 3% **7**. Recrystallization from CCl_4 followed by benzene–hexane produced 0.9 g of **6**: mp 104–105°; nmr ($CDCl_3$) δ 0.83 (d, 3, $HCCH_3$), 2.42 (s, 3, $CH_3C_6H_4$), 3.10–3.70 (m, 1, $SO_2C(H)CH_3$), 4.50 (s, 1, OH), 4.90 (d, 1, HCC_6H_5), 7.20–7.95 (m, 9, aromatic H).

***erythro*-1-Butyl-(1,1-dioxy-2-thiolanyl)carbinol (8).**—Sulfolane (24 g, 0.2 mol) in 500 ml of THF was treated with *n*-butyllithium (0.2 mol) and pivalaldehyde (17.2 g, 0.2 mol) as described above. A viscose oil was obtained which was taken up in 95% EtOH and chilled. The 2,5 diadduct (7.6 g) was obtained: mp 228–229°; nmr (d_6-DMSO) δ 0.81 (s, 18, $C(CH_3)_3$), 1.7–2.3 (m, 4, CH_2CH_2), 2.60–3.70 (m, 4, OH and $CHSO_2CH$), 4.7–5.0 (m, 2, $HCC(CH_3)_3$).

Anal. Calcd for $C_{14}H_{28}O_4S$: C, 57.50; H, 9.65; S, 10.96. Found: C, 57.69; H, 9.73; S, 11.08.

The mother liquor was stripped of solvent and recrystallized from CCl_4–petroleum ether (30–60°) to obtain 47% **8**: mp 103.5–105°; nmr ($CDCl_3$) δ 0.98 (s, 9, $C(CH_3)_3$), 1.9–2.0 (m, 4, CH_2–CH_2), 2.75 (s, 1, OH), 2.80–3.30 (m, 3, CH_2SO_2CH), 3.91 (d, J = 1, 1, $HCC(CH_3)_3$).

Anal. Calcd for $C_9H_{18}O_3S$: C, 52.40; H, 8.80; S, 15.54. Found: C, 52.33; H, 8.77; S, 15.77.

Bis-1,1-diphenyl(1,1-dioxy-2,5-thiolanyl)carbinol (13).—A solution of sulfolane (1.0 g, 8.35 mmol) in 50 ml of THF was treated with *n*-butyllithium (16.7 mmol) and benzophenone (3.04 g, 16.7 mmol) in 50 ml of THF. On acidification with HCl the diadduct **13** precipitated and was removed by filtration. Recrystallization from $CHCl_3$ resulted in 3.02 g (75% yield) of **13**, mp 312–313°.

Anal. Calcd for $C_{30}H_{28}O_4S$: C, 74.35; H, 5.82; S, 6.62. Found: C, 73.92; H, 5.65; S, 6.63.

The solvent was removed from the initial filter solution and recrystallized from ethanol. An additional 5% of **13** was obtained and 0.46 g (18% yield) of the monoadduct **14**, mp 203–204° (lit.[1d] 203.5–204.5°).

***threo*-1-Chloro-1-phenyl(1,1-dioxy-2-thiolanyl)methane (9).**—A solution of **1** (3.8 g, 16.3 mmol) in 100 ml of dry dioxane was cooled to 15° and $SOCl_2$ (4.5 g) was added. The solution was stirred at room temperature for 72 hr, and the solvent and excess $SOCl_2$ were removed *in vacuo* leaving 3.97 g (100% yield) of a 1:1 mixture of **9** and **10**. This was separated on an acid-washed Al_2O_3 column eluting with 50% $CHCl_3$ in CCl_4 to give **9**: mp 193–194°; nmr ($CDCl_3$) δ 1.40–2.32 (m, 4, CH_2CH_2), 2.80–3.90 (m, 3, CH_2SO_2CH), 5.06 (d, 1, ClCH), 7.35 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{13}ClO_2S$: C, 53.98; H, 5.35; Cl, 14.49; S, 13.10. Found: C, 54.25; H, 5.34; Cl, 14.79; S, 13.16.

***erythro*-1-Chloro-1-phenyl(1,1-dioxy-2-thiolanyl)methane (10).**—In an nmr tube was placed 0.1 g of **2** in 0.3 ml of $CDCl_3$ and 0.2 ml of $SOCl_2$. The reaction was allowed to stand in a desiccator filled with Drierite and KOH pellets. Spectra were taken periodically. After 72 hr conversion was complete. Removal of solvent left 0.106 g (98% yield) of **10**, mp 158–159°. One recrystallization from benzene–hexane gave white crystals: mp 159–160°; nmr ($CDCl_3$) δ 1.83–2.85 (m, 4, CH_2CH_2), 2.90–3.32 (m, 2, CH_2SO_2), 3.39–3.98 (m, 1, $CHSO_2$), 5.22 (d, 1, ClCH), 7.38 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}ClO_2S$: C, 53.98; H, 5.35; Cl, 14.49; S, 13.10. Found: C, 53.77; H, 5.38; Cl, 14.25; S, 13.15.

An identical reaction with **1** was complete in 12 hr and showed complete racemization to yield **9** and **10** in equivalent amounts.

Dehydrohalogenation of 10.—In an nmr tube were placed 0.1 g of **10**, 0.3 ml of $CDCl_3$, and 0.1 ml of NEt_3. After 48 hr at room temperature conversion to the *cis* olefin **15** was complete. The reaction mixture was worked up with H_2O and $CHCl_3$ and recrystallized from benzene–hexane to give 0.80 g (90% yield) of **15**: mp 83–83.5°; nmr ($CDCl_3$) δ 2.26 (p, 2, CH_2), 3.05 (t, 4, CH_2SO_2 and $CH_2C{=}C$), 7.22 (t, 1, $C{=}CH$), 7.38 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.43; H, 5.78; S, 15.61.

Similar treatment of **9** resulted in quantitative recovery of starting material after 2 weeks.

5-Chloro-1-phenyl-1-pentyne.—To a slurry of $NaNH_2$ (16.0 g) in 400 ml of liquid NH_3 was added dropwise phenylacetylene (Farchan Acetylenic Chemicals) (40.8 g, 0.4 mol). After 1 hr at reflux 1-bromo-3-chloropropane (70 g) was added and stirring was continued for 1 hr. Replacement of NH_3 with ether, acidification with dilute HCl, and distillation gave 33.1 g (47% yield) of **5-chloro-1-phenyl-1-pentyne**: bp 98–100° (0.03 mm); nmr ($CDCl_3$), δ 1.90 (p, 2, $CH_2CH_2CH_2$), 2.49 (t, 2, $C{\equiv}CCH_2$), 3.57 (t, 2, CH_2Cl), 7.02–7.58 (m, 5, C_6H_5).

Reaction of 5-Chloro-1-phenyl-1-pentyne with Thiourea.—5-Chloro-1-phenyl-1-pentyne (30 g, 0.168 mol) and thiourea (12.8 g, 0.168 mol) were refluxed in 100 ml of 95% ethanol for 24 hr. NaOH (10.1 g) in 100 ml of H_2O was added and reflux was continued 2 hr. After cooling to room temperature and extraction with benzene an 86% yield of the *trans* olefin **18** was obtained: bp 110–114° (0.02 mm); nmr ($CDCl_3$) δ 1.91 (p, 2, $CH_2CH_2CH_2$), 2.58–2.95 (m, 2, $CH_2C{=}CH$), 3.10 (t, 2, CH_2S), 6.43 (t, 1, $C{=}CH$); 6.90–7.56 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}S$: C, 74.97; H, 6.86; S, 18.16. Found: C, 74.73; H, 7.08; S, 18.06.

Oxidation of 18.—To a solution of **18** (10.0 g, 56.8 mmol) in 57 ml glacial HOAc was added 17 ml of 30% H_2O_2. The reaction was heated at reflux for 1 hr, poured on ice, extracted with $CHCl_3$, and dried (Na_2SO_4), and solvent was removed *in vacuo* leaving a yellow solid. Recrystallization from CCl_4 gave 7.3 g (62% yield) of the *trans*-vinyl sulfone **16**: mp 101–102°; nmr ($CDCl_3$) δ 2.12 (p, 2, $CH_2CH_2CH_2$), 2.79–3.27 (m, 4, CH_2SO_2 and $CH_2C{=}C$), 6.80 (t, 1, $C{=}CH$), 7.20–7.50 (m, 3, aromatic H), 7.52–7.88 (m, 2, aromatic H).

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.38; H, 5.82; S, 15.54.

Dehydration of 2.—The *erythro* alcohol **2** (3 g) was refluxed in 30 ml of 85% H_3PO_4 for 1 hr. This was poured onto ice and extracted with $CHCl_3$. Subsequent work-up and recrystallization from benzene–hexane gave 1.9 g of **15** (69% yield), mp 83–83.5°.

Registry No.—**1**, 24463-72-7; **2**, 24463-73-8; *trans*-propenyl benzene oxide, 23355-97-7; *cis*-propenyl-benzene oxide, 21884-74-2; **3**, 24463-76-1; **4**, 24463-77-2; **5**, 24463-78-3; **6**, 24463-79-4; **7**, 24463-80-7; **8**, 24515-54-6; **9**, 24463-81-8; **10**, 24463-82-9; **11**, 14195-15-4; **12**, 24463-84-1; **13**, 24463-85-2; **15**, 24463-86-3; 5-chloro-1-phenyl-1-pentyne, 24463-87-4; **16**, 24463-88-5; **18**, 24463-89-6; 2,5 diadduct, 24463-90-9.

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Hydroperoxide Oxidations Catalyzed by Metals. III. Epoxidation of Dienes and Olefins with Functional Groups

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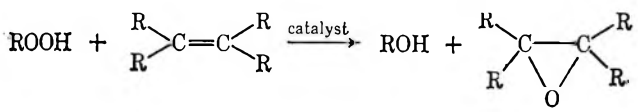
The molybdenum hexacarbonyl and the vanadyl acetylacetonate catalyzed epoxidations of olefins by organic hydroperoxides have been tried on a series of diolefins and olefins with functional groups. Molybdenum hexacarbonyl was a better catalyst for the epoxidation of all the olefinic compounds except allylic alcohols. Only with allylic alcohols did vanadyl acetylacetonate give higher yields of epoxide. A mechanism has been proposed for the allylic alcohol–vanadium catalyzed reaction.

In the first paper[1] of this series, the epoxidation of monoolefins with organic hydroperoxides catalyzed by group Vb and VIb transition metals was reported, and a mechanism for the reaction was proposed. The reaction has now been extended to a series of diolefins and olefins with functional groups.



Results

Nonconjugated Dienes.—To test the reactivity of double bonds in nonconjugated dienes, the epoxidation of 4-vinylcyclohexene and 1,4-hexadiene was carried out. It was found that these compounds were similar in reactivity to monoolefins.[1] As more alkyl substituents are bonded to the carbon atoms of the double bond, the reactivity of the double bond increases. Thus, with 4-vinylcyclohexene, only the ring olefin was epoxidized, and, with 1,4-hexadiene, the internal epoxide was the predominant product. When the pure *cis*- and *trans*-1,4-hexadienes were allowed to react separately, the *cis* isomer showed an 11 to 1 preference for internal epoxidation, and the *trans* isomer showed a 6 to 1 preference. The greater ratio of internal to terminal epoxide for the *cis* olefin is probably due primarily to the steric effect, although the energy difference between the *cis* and *trans* isomer may also be important.

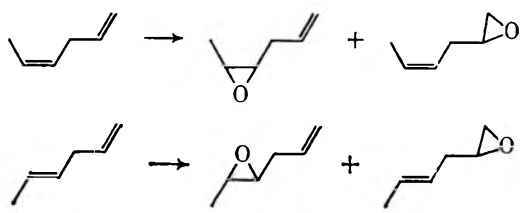


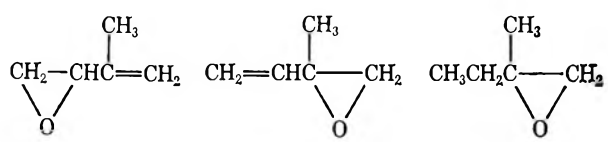
Table I summarizes the experimental conditions and the yields of monoepoxides obtained with various dienes using a 2:1 molar ratio of diene to hydroperoxide. Previous work[1] has shown that this ratio assures a high yield of epoxide. Some diepoxide also formed in these reactions. The yield of diepoxide varied from less than 1% for 4-vinylcyclohexene to 13% for dicyclopentadiene. The amount of diepoxide can be decreased further by using a higher ratio of diene to hydroperoxide.

(1) N. N. Sheng and J. G. Zajacek, *Advan. Chem. Ser.*, **76**, 418 (1968).

The synthesis of diepoxide from nonconjugated dienes was also investigated. First, the monoepoxide was made and isolated. It was then allowed to react with more hydroperoxide using a ratio of unsaturated epoxide to hydroperoxide of 2:1 or higher. The experimental conditions and results are shown in Table II.

endo-Dicyclopentadiene was unique among the dienes since the double bonds are very reactive and the epoxides are very stable. Steric effects would be expected to prevent *trans* nucleophilic attack on both epoxide rings, and *cis* nucleophilic ring opening should be a slow reaction. Since both double bonds are easily epoxidized, the diepoxide can be made in high yield in one step with molar quantities of reagents. To obtain the diepoxide with no monoepoxide contaminant, at atmospheric pressure, the *t*-butyl alcohol must be removed as it forms. These data are shown in Table III.

Conjugated Dienes.—Conjugated dienes can also be epoxidized by this method. The reactivity of the individual double bonds in the diene again depends on the alkyl group substituents. Overall, the reactivity of the dienes studied is less than compounds containing isolated double bonds. This was shown in a competitive experiment using equimolar quantities of isoprene and 2-methyl-1-butene. At partial hydroperoxide conversion, the yield of the epoxide based on the hydroperoxide converted was quantitative, and the ratio of the three epoxides, 2-methyl-3,4-epoxy-1-butene, 3-methyl-3,4-epoxy-1-butene, and 2-methyl-1,2-epoxybutane, was 1:3.7:4.7. Typical experimental results with other conjugated dienes are shown in Table I.



With butadiene, the formation of polymeric materials was observed. This could be prevented by the addition of free-radical inhibitors. The butadiene monoepoxide yield, based on the hydroperoxide conversion, did not change in the presence or absence of a free-radical inhibitor. It changed, however, based on the diene, indicating that only the diene is involved in the polymer formation.

The hydroperoxide epoxidation of isoprene gives both 3,4-epoxy-3-methyl-1-butene and 3,4-epoxy-2-methyl-1-butene in a 4:1 molar ratio. The epoxidation of

TABLE I

EPOXIDATION OF DIENES

Olefin (mol)	Hydroperoxide (mol)	$Mo(CO)_6$, g	Temp, °C	Time, min	Conversion,[a] %	Yield,[b] %	Product[c] (ratio)
			Nonconjugated Dienes				
cis-1,4-Hexadiene (a) (0.18)	Cumene (0.07)	0.03	85	50	100	90	A:B (11:1)
trans-1,4-Hexadiene (b) (0.18)	Cumene (0.07)	0.03	85	75	94	93	C:D (6:1)
1,7-Octadiene (c) (0.10)	*t*-Butyl (0.05)	0.02	90	240	88	86	
4-Vinylcyclohexene (d) (0.10)	*t*-Butyl (0.05)	0.02	85	75	75	95	E
1,4-Cyclohexadiene (e) (0.10)	*t*-Butyl (0.05)	0.02	90	30	92	78	
1,5-Cyclooctadiene (f) (1.0)	*t*-Butyl (0.50)	0.10	80	60	100	82	
Dicyclopentadiene[d] (g) (0.05)	*t*-Butyl (0.025)	0.02	85	60	97	87	F:G (1.1:1)
			Conjugated Dienes				
Butadiene[e] (h) (0.58)	*t*-Butyl (0.17)	0.04	100	40	97	85	
1,3-Pentadiene (i) (0.03)	Cumene (0.007)	0.003	80	60	71	91	H:I (2:1)
Isoprene (j) (0.03)	*t*-Butyl (0.01)	0.003	90	64	97	84	J:K (4:1)

[a] Conversion of the hydroperoxide. [b] Yield of monoxide based on hydroperoxide converted. [c] A, *cis*-4,5-epoxy-1-hexene; B, *cis*-1,2-epoxy-4-hexene; C, *trans*-4,5-epoxy-1-hexene; D, *trans*-1,2-epoxy-4-hexene; E, 1,2-epoxy-4-vinylcyclohexane; F, 8,9-epoxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]dec-4-ene; G, 4,5-epoxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene; H, 3,4-epoxy-1-pentene; I, 1,2-epoxy-3-pentene; J, 3-methyl-3,4-epoxy-1-butene; K, 2-methyl-3,4-epoxy-1-butene. [d] Benzene (12 ml) was used as solvent. [e] Benzene (60 ml) was used as solvent and hydroquinone (0.03 g) was added as inhibitor.

TABLE II

EPOXIDATION OF NONCONJUGATED DIENE MONOXIDES

Olefin (mol)	*t*-Butyl hydroperoxide, mol	Solvent (ml)	$Mo(CO)_6$, g	Temp, °C	Time, min	Conversion,[a] %	Yield,[b] %
1,2-Epoxy-4-vinylcyclohexene (a) (0.12)	0.06		0.03	85	60	96	83
1,2-Epoxy-5-cyclooctene (b) (2.0)	1.0	Toluene (300)	0.15	100	300	100	54
Dicyclopentadiene monoxides[c] (c and c′) (0.05)	0.025	Benzene (12)	0.02	85	120	89	89
cis-1,4-Hexadiene monoxides[d] (d[e] and d′[f]) (0.02)	0.01	Benzene (2)	0.01	100	120	65	77

[a] Conversion of hydroperoxide. [b] Based on the hydroperoxide converted. [c] A 1.1:1 molar mixture of the two monoxides. [d] A 15:1 molar mixture of the internal and terminal epoxides. [e] Internal epoxide. [f] Terminal epoxide.

isoprene by the bromohydrin method[2] or by perbenzoic acid[3] gave only the 3,4-epoxy-3-methyl-1-butene. The 3,4-epoxy-2-methyl-1-butene was isolated and identified by nmr, elemental analysis, and oxirane titration. To obtain high yields of the isoprene epoxides, all the reactants must be anhydrous. It was found that 3,4-epoxy-3-methyl-1-butene reacts very rapidly with water even at room temperature to give the diol. This proves to be a convenient method for isolating the 3,4-epoxy-2-methyl-1-butene from 3,4-epoxy-3-methyl-1-butene. If the epoxidation mixture was washed with water, the 3,4-epoxy-3-methyl-1-butene was converted to the diol and dissolved in the water layer while 3,4-epoxy-2-methyl-1-butene remained in the organic layer from which it was isolated by fractional distillation.

Allylic Compounds.—This epoxidation technique was tried on a variety of allylic compounds. The results are shown in Table IV. The epoxidation of these compounds was more difficult than compounds with isolated double bonds. This would be expected based on the electrophilic mechanism proposed for this reaction. Allylic compounds which have weaker electron-withdrawing groups such as chlorides and ethers give a faster reaction and a higher yield of epoxide than those which have stronger electron-withdrawing groups such as esters and nitriles. Substitution of an alkyl group on the double bond again increased the reaction rate and the yield of the epoxide. With these compounds, a molar ratio of olefin to hydroperoxide higher than 2:1 increased the yield of the epoxides. For some of the more reactive compounds, the addition of free-radical inhibitors also increased the epoxide yield.

(2) E. J. Reist, J. G. Junge, and B. R. Baker, *J. Org. Chem.*, **25**, 1674 (1960).

(3) R. Pummerer and W. Reindel, *Ber.*, **66**, 335 (1933).

TABLE III

EPOXIDATION OF DICYCLOPENTADIENE[a]

Expt no.	*t*-Butyl hydroperoxide, mol	Time, hr	Conversion,[b] %	Yield, %[c] Monoxide	Yield, %[c] Dioxide
1	0.025	1	97	87	13
2	0.050	1	84	73	27
3	0.050	1.5	95	66	32
4	0.075	1.5	82	53	47
5	0.075	2	88	48	50
6	0.075	3	94	35	65
7	0.100	2	77	33	66
8	0.100	3	86	17	80
9	0.113	2.5	100	0	86

[a] In expt 1–8 reagents were *t*-butyl hydroperoxide (as indicated), 0.05 mol of dicyclopentadiene, 0.02 g of $Mo(CO)_6$, and 10 g of benzene; reflux temperature for this mixture is 85°. In expt 9 reagents were the same except 30 g of toluene was used as solvent and *t*-butyl alcohol was removed as it formed to keep the temperature at 100°. [b] Conversion of hydroperoxide. [c] The epoxide yield is based on hydroperoxide converted.

Allylic Alcohols.—The epoxidation of allylic alcohols gave unexpected results. With other olefinic compounds, molybdenum-catalyzed reactions, in general, gave a higher yield of epoxide than the reaction catalyzed by vanadium. Vanadium catalysts, however, gave faster reactions and higher epoxide yields in the case of allyl alcohol. With allyl alcohol and vanadium catalyst, a stoichiometric amount of olefin and hydroperoxide or an excess of hydroperoxide can be used, and high yields of the epoxide are still obtained. For other

TABLE IV
EPOXIDATION OF ALLYL COMPOUNDS

Olefin (mol)	t-Butyl hydroperoxide, mol	Benzene, ml	$Mo(CO)_6$, g	Temp, °C	Time, min	Conversion,[a] %	Yield,[b] %
Allyl ethyl ether (a) (0.023)	0.005	2	0.01	95	30	73	77
Diallyl ether (b) (0.15)	0.050		0.02	95	120	89	85
Dimethallyl ether (c) (0.25)	0.125	50	0.10	93	60	84	70
Allyl glycidyl ether (d) (0.20)	0.070	12	0.03	100	180	88	58
Dimethallyl ether monoxide[c] (e) (0.05)	0.016	10	0.008	95	90	65	68
Ethyl methacrylate[d] (f) (0.08)	0.006	5	0.006	80	180	61	72
1-Cyclohexenyl acetonitrile (g) (0.41)	0.280	30	0.15	110	60	100	41
Allyl chloride (h) (0.08)	0.005		0.01	85	120	63	75
Methallyl chloride (i) (0.08)	0.010		0.01	85	120	100	89
1,4-Dichlorobutene-2 (j) (0.10)	0.030		0.01	90	90	84	21

[a] Conversion of hydroperoxide. [b] The epoxide yield is based on the conversion of hydroperoxide. [c] 2-Methyl-2,3-epoxypropyl 2-methyl-2-propenyl ether. [d] Diphenylamine (0.03 g) was added as free-radical inhibitor.

TABLE V
EPOXIDATION OF ALLYLIC ALCOHOLS

Olefin (mol)	t-Butyl hydroperoxide, mol	Catalyst (g)	Temp, °C	Time, min	Hydroperoxide conversion, %	Epoxide[a] yield, %
Allyl alcohol (a) (0.07)	0.01	$Mo(CO)_6$ (0.01)	100	60	100	10
(0.07)	0.01	$VO(acac)_2$ (0.01)	100	25	92	83
(0.01)[b]	0.01	$VO(acac)^2$ (0.01)	100	120	88	78
(0.01)[b]	0.015	$VO(acac)^2$ (0.01)	100	180	89	64
Methallyl alcohol (b) (0.06)	0.004	$VO(acac)^2$ (0.01)	80	30	97	100
(0.06)	0.004	$Mo(CO)_6$ (0.01)	80	30	82	69
2-Methyl-1-penten-3-ol (c) (0.04)	0.004	$VO(acac)_2$ (0.01)	80	30	94	100[c]
(0.04)	0.004	$Mo(CO)_6$ (0.01)	80	30	94	100[c]
4-Methyl-4-penten-2-ol (d) (0.04)	0.004	$VO(acac)_2$ (0.01)	80	30	88	100[c]
(0.04)	0.004	$Mo(CO)_6$ (0.01)	80	30	90	83[c]
5-Hexen-2-ol (e) (0.04)	0.004	$VO(acac)_2$ (0.01)	80	30	7	51[d]
(0.04)	0.004	$Mo(CO)_6$ (0.01)	80	30	69	86[d]
2-Cyclohexen-1-ol (f) (0.02)	0.002	$VO(acac)_2$ (0.01)	80	30	85	51[d]
(0.02)	0.002	$Mo(CO)_6$ (0.01)	80	30	62	95[d]
1,5-Hexadien-3-ol (g) (0.04)	0.004	$VO(acac)_2$ (0.01)	80	30	77	92[e]
(0.04)	0.004	$Mo(CO)_6$ (0.01)	80	30	91	75[e]
3,4-Dihydroxylbutene-1 (h) (0.03)	0.01	$VO(acac)_2$ (0.005)	80	60	87	60
3-Methyl-3,4-dihydroxylbutene-1 (i) (0.05)	0.01	$VO(acac)_2$ (0.01)	80	60	84	91

[a] Epoxide yield is based on the hydroperoxide conversion. [b] Tetrahydrofuran (2 g) was used as solvent in these experiments. [c] The epoxide for 2-methyl-1-penten-3-ol is a 10:1 (vanadium catalyst) and a 4:1 (molybdenum catalyst) ratio of the two possible optical racemic pairs based on vpc retention times; for 4-methyl-4-penten-2-ol, the epoxide is a 1:2 (vanadium catalyst) and a 1:1 (molybdenum catalyst) mixture based on vpc retention times. [d] The two optical racemic pairs were not separated by vpc. [e] The epoxide is a 4:1 mixture of 1,2-epoxy-3-hydroxyl-5-hexene and 1,2-epoxy-4-hydroxyl-5-hexene for the vanadium-catalyzed reaction; for the molybdenum-catalyzed reaction, the epoxide is a 1:1 mixture.

olefins a 2:1 molar ratio of the olefin to hydroperoxide is best for maximum epoxide yields. The experimental results on the epoxidation of various allylic and unsaturated alcohols are summarized in Table V. These data show that there are three variables which determine whether vanadium or molybdenum compounds give a higher yield of epoxide. These variables are the presence or absence of an alkyl group on the double bond of the unsaturated alcohol and on the carbinol carbon, and the position of the hydroxyl group relative to the double bond. Substitution of an alkyl group on the double bond, as in methallyl alcohol, allows the reaction to be run at a lower temperature, and the molybdenum catalyst gives only a slightly lower yield of epoxide than the vanadium catalyst. With substitution of an alkyl group on the double bond and the carbinol carbon in 2-methyl-1-penten-3-ol and 4-methyl-4-penten-2-ol, the molybdenum- and vanadium-catalyzed reactions gave comparable epoxide yields. As the position of the hydroxyl group relative to the double bond changes as in 5-hexen-2-ol, the olefin becomes more like an unsubstituted olefin, and the molybdenum-catalyzed reaction gives both a higher conversion of the hydroperoxide and a higher yield of the epoxide.

If optically active unsaturated alcohols had been used, the epoxidation reaction would give two optically active epoxides. In the case of 2-methyl-1-penten-3-ol and 4-methyl-4-penten-2-ol, starting with the racemic mixture of the unsaturated alcohol, the gas chromatograph separated the two optical racemic pairs of epoxides. The ratio of the racemic pairs varied with the hydroxyl position and whether the catalyst was molybdenum or vanadium. The racemic pairs were separated by preparative gas chromatography and were shown to be epoxides by nmr and ir. Unambiguous identification of the stereochemistry of the two isomeric pairs was not possible by nmr.

1,5-Hexadien-3-ol was epoxidized with molybdenum and vanadium catalysts to see which double bond would be epoxidized. In the vanadium-catalyzed reaction, vpc analysis showed that the epoxide was a 4:1 mixture

of 1,2-epoxy-3-hydroxyl-5-hexene (I) and 1,2-epoxy-4-hydroxyl-5-hexene (II) and, in the molybdenum-catalyzed reaction, was a 1:1 mixture of these epoxides. Compound I had the shorter retention time on the vpc. These epoxides were separated by preparative vpc and identified by nmr and mass spectrometry.

Discussion

From previous studies on the epoxidation of olefins,[1] the results obtained in the vanadium-catalyzed epoxidation reactions of allylic alcohols, especially allyl alcohol and 1,5-hexadien-3-ol, were unexpected. In the epoxidation of simple olefins, molybdenum catalysts always gave higher yields of epoxides.

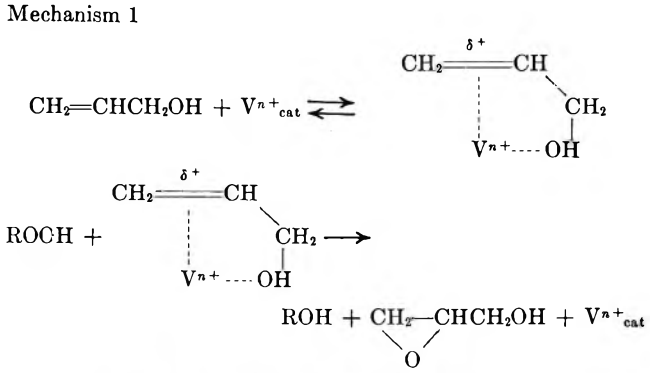
Since allylic olefins should be less reactive than simple olefins, vanadium compounds should not have been good catalysts for any epoxidation reactions under the experimental conditions reported in this paper. Since the vanadium compounds were good catalysts for the epoxidation of allylic alcohols, the original mechanism proposed for this epoxidation reaction[1,4] must be modified slightly to fit these new data. Alcohols have been observed to retard the rate of the epoxidation reaction, and a metal compound–alcohol complex has been postulated to explain these results. The kinetic studies[1] with molybdenum hexacarbonyl have been made to over 70% hydroperoxide conversion and showed no deviation due to molybdenum–alcohol complexing. Only when alcohols are used as solvents is the retardation observed with molybdenum catalyst. However, kinetic studies[4] under comparable conditions with vanadyl acetylacetonate showed a very marked retardation by alcohol. These two studies indicate that the alcohol formed in the epoxidation reaction complexes better with the vanadium than the molybdenum catalyst. This evidence would indicate that an allylic alcohol–vanadium catalyst complex should form quite readily. Three mechanisms can be postulated to explain the epoxidation of the allylic alcohols.

In mechanism 1, both the hydroxyl group and the double bond of the allyl alcohol complex with the vanadium catalyst. In this complex the double bond would have a partial positive charge and then could be epoxidized by a nucleophilic hydroperoxide. This mechanism is similar to the base-catalyzed epoxidation of α,β-unsaturated ketone by the hydroperoxide.[5] If this were the mechanism for the reaction, methallyl alcohol for electronic and steric effects should be less reactive than allyl alcohol. The results show that the opposite is true. Methallyl alcohol is epoxidized at a lower temperature than allyl alcohol.

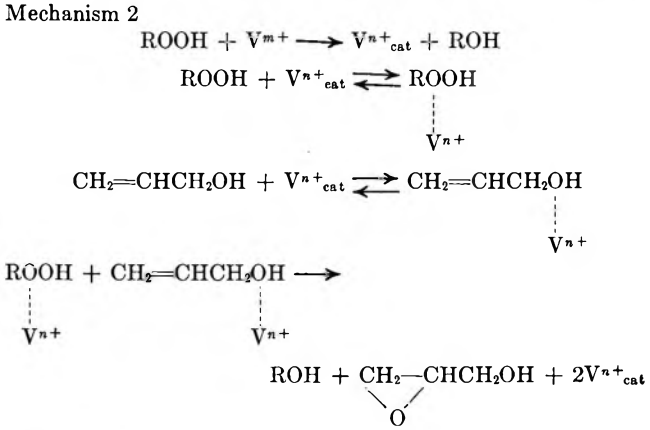
Mechanism 2 shows that the hydroxyl group of the allyl alcohol first complexes with the vanadium. This complex is then epoxidized by the hydroperoxide–vanadium intermediate. This mechanism would not explain why vanadium complexing with the hydroxyl group of the allyl alcohol should give a high epoxide yield compared with molybdenum. Also it would not explain why the allylic double bond was preferentially epoxidized in 1,5-hexadien-3-ol.

Mechanism 3 shows that the hydroperoxide (or the allyl alcohol)–vanadium intermediate, which forms first, has to further complex with the allyl alcohol (or the hydroperoxide), before the double bond is epoxidized. This mechanism is most consistant with the experimental observation. The allyl alcohol–hydroperoxide–vanadium complex should be more stable than the hydroperoxide–vanadium complex. The geometry of the intermediate complex would place the electron-deficient oxygen of the hydroperoxide in the vicinity of the double bond. This makes the epoxidation reaction favored over the decomposition of the hydroperoxide. Inserting additional carbon atoms between the double bond and the hydroxyl group destroys this favorable geometry for the epoxidation reaction. Thus, 1,5-hexadien-3-ol gave 1,2-epoxy-3-hydroxy-5-hexene as the major product, and 5-hexen-2-ol gave only a poor yield of the epoxide.

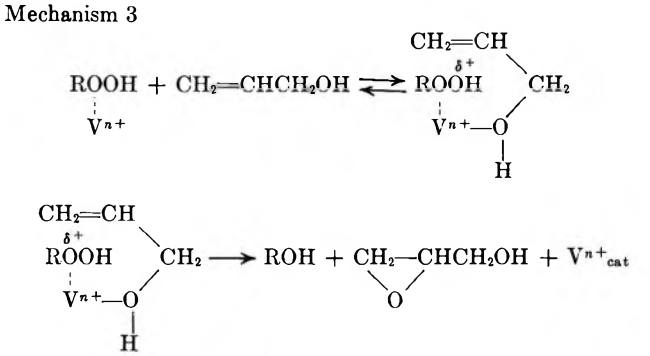
Mechanism 1



Mechanism 2



Mechanism 3



Further studies on the kinetics and the stereochemistry of the vanadium-catalyzed epoxidation of allylic alcohols are in progress in order to learn more about this reaction.

Experimental Section

General Procedure.—Infrared spectra data were obtained with a Perkin-Elmer infracord; nmr data, with a Varian A-60; and

(4) E. S. Gould, R. R. Hiatt, and K. C. Irwin, *J. Amer. Chem. Soc.*, **90**, 4573 (1968).

(5) N. C. Yang and R. A. Finnegan, *ibid.*, **80**, 5845 (1958).

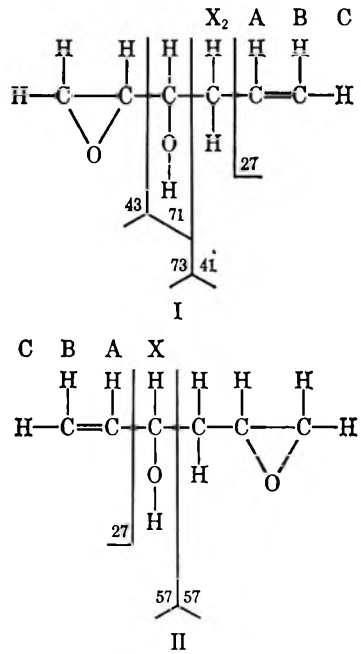
the mass spectra data, on a Consolidated Electrodynamics Corp. Model 104 at 70 eV. Gas–liquid partition chromatography was done using either a Varian Aerograph Model 90-P or a Perkin-Elmer Model 226. The column used in the Aerograph was 10 ft × .25 in. packed with 20% Carbowax 20M on 30–60 mesh acid-washed firebrick. The stainless steel capillary column used in the Perkin-Elmer chromatograph was 100 ft × 0.02 in. coated with Carbowax 15–40M. Hydroperoxide concentration was analyzed by standard titration procedure.[6] Epoxide concentration was analyzed by vpc. All epoxides were identified by comparison (vpc retention and ir and nmr spectra) with authentic samples. Reagent grade chemicals were used when available without further purification. Commercially available cumene hydroperoxide was purified according to Davies.[7] *t*-Butyl hydroperoxide (94% purity) was obtained from the Lucidol Division, Wallace and Tiernan, Inc., and purified to 97% by drying over anhydrous magnesium sulfate. Olefins were purified by distillation.

Isoprene.—A solution of 45 g of cumene hydroperoxide (99+% purity), 110 g of isoprene, and 0.1 g of $Mo(CO)_6$ was charged into a 500 ml Magnedrive autoclave (Pressure Product Co.) and heated to 80–82° for 35 min. The reactor was cooled to room temperature. The products were collected and were analyzed for hydroperoxide by standard iodometric titration and epoxides by vpc. There was a 97% conversion of the hydroperoxide and 92% yield of two isomeric epoxides based on the conversion of hydroperoxide. The two epoxides were 3,4-epoxy-3-methyl-1-butene and 3,4-epoxy-2-methyl-1-butene in a ratio of 4:1. Spinning-band distillation gave two fractions with bp 79–80 and 80–84°.

The ratio of 3,4-epoxy-3-methyl-1-butene and 3,4-epoxy-2-methyl-1-butene was 7.9:1 in the fraction of bp 79–80°, 2.4:1 in the one of bp 80–84°. With the first fraction, 3,4-epoxy-3-methyl-1-butene was identified by comparison (vpc retention and ir and nmr spectra) with an authentic sample prepared by the bromohydrin method.[2] With the second fraction, the pure 3,4-epoxy-2-methyl-1-butene was isolated by preparative vpc. It was identified by nmr (τ 4.83, 5, 6.65, 7.25, 8.37), elemental analysis (Calcd: C, 71.50; H, 9.50; O, 19.05. Found: C, 71.58; H, 9.37; O, 19.08.), and oxirane titration.[8]

Allyl Alcohol.—A solution of 4.1 g of allyl alcohol, 0.95 g of *t*-butyl hydroperoxide (95%), and 0.01 g of vanadyl acetylacetonate was sealed in a pressure tube and allowed to react for 25 min in a constant-temperature bath at 100°. The tube was removed and cooled. Hydroperoxide and epoxide were analyzed by iodometric titration and vpc. There was a 92% conversion of the hydroperoxide and an 83% yield of the epoxide based on the hydroperoxide conversion.

1,5-Hexadien-3-ol.—A solution of 19.6 g of 1,5-hexadien-3-ol, 9.0 g of *t*-butyl hydroperoxide (97% purity), and 0.01 g of vanadyl acetylacetonate was heated for 30 min at 80° in a three-necked flask equipped with a condensor, magnetic stirrer, and a thermometer. Fractional distillation on a Nester–Faust spinning-band gave 1,2-epoxy-3-hydroxyl-5-hexene [bp 45° (1 mm)] in 93% purity. The remainder of the cut was 1,2-epoxy-4-hydroxyl-5-hexene. An identical run with 0.01 g of molybdenyl acetylacetonate as catalyst followed by fractional distillation gave 1,2-epoxy-4-hydroxyl-5-hexene [bp 53° (1 mm)] in 85% purity. The remainder of the cut was 1,2-epoxy-3-hydroxyl-5-hexene. The nmr spectra of these epoxides exhibit resonances corresponding to a terminal olefin, a terminal epoxide, and a $-CH_2CHOH$ group. In both cases, the position of the hydroxyl group is clearly indicated by the splitting patterns of the epoxide and olefinic protons. For compound I, the olefinic proton appears as the ABC part of an $ABCX_2$ system with J_{AX} = 6.8 Hz, while compound II appears as the ABC part of an ABCX system



I

II

with J_{AX} = 5.6 Hz. The mass spectra (70 eV) showed a large ion intensity at *m/e* 43 ($C_2H_3O^+$) and 57 ($C_3H_5O^+$) for compounds I and II, respectively. Some basic characteristic peaks of these two compounds are listed in Table VI.

TABLE VI

CHARACTERISTIC MASS SPECTRA OF COMPOUNDS I AND II

m/e	Intensity of I	Intensity of II
43[a]	100	24
57[a]	10	100
27	68	86
31	22	47
55	54	34
69	15	4
73	11	3
71	8	3
96	7	3

[a] Base peak for compounds I and II, respectively.

Registry No.—I, 24058-61-5; II, 24058-62-6; molybdenum hexacarbonyl, 13939-06-5; vanadyl acetylacetonate, 13930-95-5; Table I—a, 7318-67-4; b, 7319-00-8; c, 3710-30-3; d, 100-40-3; e, 628-41-1; f, 111-78-4; g, 77-73-6; h, 106-99-0; i, 504-60-9 j, 78-79-5; Table II—a, 106-86-5; b, 637-90-1; c, 4387-46-6; c′, 4387-45-5; d, 14031-68-6; d′, 24578-16-3; Table IV—a, 557-31-3; b, 557-40-4; c, 628-56-8; d, 106-92-3; e, 24058-76-2; f, 97-63-2; g, 6975-71-9; h, 107-05-1; i, 563-47-3; j, 764-41-0; Table V—a, 107-18-6; b, 513-42-8; c, 2088-07-5; d, 2004-67-3; e, 626-94-8; f, 822-67-3; g, 924-41-4; h, 497-06-3; i, 24058-88-6.

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Solvomercuration–Demercuration. I. The Oxymercuration–Demercuration of Representative Olefins in an Aqueous System. A Convenient Mild Procedure for the Markovnikov Hydration of the Carbon–Carbon Double Bond

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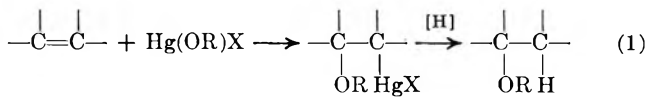
The reaction of olefins with mercuric acetate in aqueous tetrahydrofuran, followed by the *in situ* reduction of the mercurial intermediate by alkaline sodium borohydride, provides a highly convenient procedure for the Markovnikov hydration of the carbon–carbon double bond. The synthesis has been applied to a representative selection of olefins. It was observed that mono-, di-, tri-, and tetraalkyl, as well as phenyl-substituted olefins, undergo hydration readily by this procedure to give high yields of the Markovnikov alcohol, generally in excess of 90%. The reaction displays high specificity and sensitivity to steric factors, and advantage of these characteristics can be taken to achieve desired syntheses.

The hydroboration–oxidation of olefins provides a highly convenient procedure, without evident rearrangement, for achieving the anti-Markovnikov hydration of carbon–carbon double bonds.[3,4] For some time we had felt the need in our synthetic work for an equally mild procedure, equally free of rearrangement, for the Markovnikov hydration of carbon–carbon double bonds. Preliminary studies indicated that the oxymercuration of olefins in aqueous tetrahydrofuran, followed by *in situ* reduction of the organomercurial by alkaline sodium borohydride, offered great promise for this requirement.[5] Accordingly, we undertook a detailed study of the scope of this reaction. The results of that study are reported in the present paper.

It shortly became apparent that this convenient, combined procedure should be capable of very wide variation, and serve as a general technique for the introduction of a wide variety of nucleophiles to carbon–carbon double bonds in the Markovnikov direction. Thus, we have developed procedures for the synthesis of ethers[6] and amines,[7] and others have utilized the technique for the synthesis of alkyl azides[8] and peroxides.[9] Consequently, we have generalized our initial interest in oxymercuration–demercuration to solvomercuration–demercuration, and this more general interest is expressed in the title of this new series.

The oxymercuration reaction was originally explored by Hofmann and Sand, beginning in 1900.[10] Although an enormous number of studies of the reaction have appeared in the literature, these later papers have concerned themselves primarily with the mechanism of the reaction and the stereochemistry of the products.[11]

Stoichiometrically the oxymercuration reaction consists in the addition of a mercuric salt or of the elements of a mixed mercuric salt, Hg(OR)X, to an olefinic double bond. Reduction of the carbon–mercury bond (demercuration) gives the corresponding alcohol, ether, or ester.



(1)

At the time our systematic study was undertaken the usual procedure involved addition of a mercuric salt, HgX_2 (X = OAc, NO_3, ClO_4, etc.), or mercuric oxide and an acid (HNO_3, $HClO_4$, etc.) to an aqueous (R = H), alcoholic (R = alkyl), or acidic (R = acyl) solution of the olefin. The resulting mixture was stirred for times ranging from a few minutes to several days. Not infrequently, it was recommended that catalysts, such as strong acids,[12] peroxides,[12] boron trifluoride, etc., be used to enhance the rate.

It is puzzling why so many workers used such long reaction times. For example, Traylor and Baker[13] prepared norbornylmercuric acetate in 61% yield from the olefin by stirring the reagents (norbornene, mercuric oxide, and mercuric acetate) for 30 hr. In contrast, a reaction time of 30 sec was adequate to achieve a 100% yield in the conversion of norbornene to *exo*-norborneol by the present procedure.[14] Moreover, we have discovered that, not only are such long reaction times less convenient, but not infrequently they are actually deleterious and result in greatly decreased yields.

From the work of Hofmann and Sands, it is known that, in the case of simple olefins, the reaction proceeds in the Markovnikov sense (that is, by placing the mercury atom on the carbon atom having the more hydrogen) to give an almost quantitative yield of product. However, it has been reported that side reactions often interfere, leading to polymers,[11a] dialkylmercurials,[11a]

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and products of oxidation[15] and substitution.[11a] Fortunately, these side reactions do not appear to be important under the conditions adopted for our hydration. Perhaps the much shorter reaction times utilized in our procedure contribute importantly in circumventing the appearance of these undesired side reactions.

Reduction of the carbon–mercury bond has been achieved using a number of reagents, including sodium–mercury amalgam, hydrazine, lithium aluminum hydride, and various borohydrides.[13,16,17] In practically all of the earlier work the initial oxymercuration product was precipitated as the chloride and this intermediate reduced in a separate operation. It was the recognition that oxymercuration could be accomplished very rapidly and essentially quantitatively in aqueous tetrahydrofuran (eq 2) and that the mercury could be removed *in situ* in a second fast reaction by treatment with alkaline sodium borohydride (eq 3) that persuaded us that this was the convenient Markovnikov hydration procedure that would complement the convenient anti-Markovnikov hydration procedure based on hydroboration–oxidation.

$$\mathrm{RCH{=}CH_2} + \mathrm{Hg(OAc)_2} \xrightarrow[25^\circ,\ \sim 10\ \mathrm{min}]{50{:}50\ \mathrm{THF{-}H_2O} } \underset{\mathrm{OH}}{\mathrm{RCHCH_2HgOAc}} \quad (2)$$

$$\underset{\mathrm{OH}}{\mathrm{RCHCH_2HgOAc}} \xrightarrow[25^\circ]{\mathrm{NaOH,\ NaBH_4}} \underset{\mathrm{OH}}{\mathrm{RCHCH_3}} + \mathrm{Hg} \quad (3)$$

Results and Discussion

It was our objective to develop a synthetic procedure for the Markovnikov hydration of the carbon–carbon double bond *via* oxymercuration–demercuration which would be simple in application and conducive to simple analysis and/or isolation of the products. The oxymercuration stage requires the addition of a water-soluble mercuric salt with a (generally) water-insoluble olefin. It is evident that a nucleophilic cosolvent might compete with water for the intermediate mercury species, giving a mixed product. Consequently, we chose a water–tetrahydrofuran (THF) solvent system in order to realize both the benefits of homogeneity (or near homogeneity) of the system and the inertness of the cosolvent.

Organomercuric salts are generally soluble, as the organomercuric hydroxides, in strongly alkaline solutions, and also quite stable in such solutions. Moreover, Bordwell and Douglass[16c] established that sodium borohydride reduces alkylmercuric salts or hydroxides both rapidly and smoothly in either neutral or alkaline solutions. In view of the greater solubility of the alkylmercuric hydroxide and the enormously greater stability of sodium borohydride in strongly alkaline solutions, we decided to utilize alkaline sodium borohydride for the *in situ* reduction. This worked ideally.

Mercuric acetate dissolves in water to give a clear solution. When 50 vol % of THF is added, a finely divided yellow precipitate appears. Presumably this is mercuric oxide or a basic mercuric acetate, although we have not attempted to establish the composition. Upon addition of the olefin this yellow precipitate or suspension disappears and a clear, colorless solution usually results, frequently in a matter of minutes or even seconds. In order to determine whether the time for disappearance of the yellow color (T_1) can be correlated to the extent of reaction, several olefins were oxymercurated and base was added immediately following the disappearance of the yellow color to stop further oxymercuration. The reaction mixture was then treated with sodium borohydride solution and analyzed for alcohol. The results are presented in Table I.

TABLE I

CORRELATION OF T_1 WITH EXTENT OF REACTION[a]

Olefin	T_1[b]	Yield of alcohol,[c] %
2-Methyl-2-butene	10 sec	61
Cyclohexene	55 sec	65
3,3-Dimethyl-1-butene	2 min	60
1-Dodecene	7 min	49

[a] Reaction run under standard conditions, as described in text. [b] Time for disappearance of the yellow color. [c] By glpc analysis. Markovnikov isomer only.

Some small variation in T_1 is observed from run to run, presumably because the reaction mixture is heterogeneous at the start of the reaction. However, the data indicate that the reaction has gone to approximately 60% of completion when all of the yellow precipitate or suspension has vanished. Although this may only be true for reactions carried out in a 1:1 THF–water solvent system, it should be approximately valid for other solvent ratios. In any event, the change in color provides a highly convenient, albeit approximate, measure of the reaction rate.

Using T_1 as an indication of the extent of reaction, the effect of solvent composition on the reaction was studied. 3,3-Dimethyl-1-butene (10 mmol) was added to the yellow suspension resulting from mixing 10 mmol of mercuric acetate and the volumes of water and THF indicated in Table II. The wide variation of T_1 with change in solvent composition demonstrates the desirability of selecting the proper solvent system to obtain optimum results.

TABLE II

THE EFFECT OF SOLVENT COMPOSITION ON THE RATE OF OXYMERCURATION OF 3,3-DIMETHYL-1-BUTENE

Vol of water, ml	Vol of THF, ml	T_1,[a] min
5	20	90
10	20	15
10	10	2
20	10	2
20	5	6

[a] Time for disappearance of the yellow color.

The effect of the THF to water ratio of the solvent system on the oxymercuration of 1-hexene and 1-octa-

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(17) For a more complete discussion, with pertinent references, see Bordwell and Douglass.[16c] The use of borohydrides for demercuration appears to have been introduced by Henbest and Nicholls,[16a] whereas Robson and Wright[16b] and Traylor and Baker[13] appear to have first used borohydride in aqueous solution for demercuration. However, we are indebted to Bordwell and Douglass[16c] for the first detailed study of such reductions in aqueous media and the recording of the great speed of that reaction.

decene was studied. The olefin, 10 mmol, was added to 10 mmol of mercuric acetate in 10 ml of water with either 10, 20, or 30 ml of THF. At the end of the appropriate interval of time, alkaline sodium borohydride was introduced to reduce the organomercurial. The variation of yield with time is given in Table III.

TABLE III
EFFECT OF THF TO WATER RATIO ON THE YIELD OF 2-HEXANOL AND 2-OCTADECANOL

Solvent composition, THF:H_2O	Time of reaction, hr	Yield of 2-hexanol, %	Yield of 2-octadecanol %
1:1	0.25	94	16
	1.0	95	48
	8.0	93	76
	24.0	96	93
2:1	0.25	92	82
	1.0	91	95
	8.0	93	92
	24.0	91	95
3:1	0.25	85	86
	1.0	83	93
	8.0	86	93
	24.0	90	96

From these results it is apparent that the reaction of the low molecular weight olefin, 1-hexene, is both rapid and quantitative. The yield of 2-hexanol is slightly lower in the 3:1 THF–water solvent system. The high molecular weight olefin, 1-octadecene, clearly shows the advantages of a less aqueous system in this case. The much slower reaction of 1-octadecene in the more aqueous solvents is presumably due to its very limited solubility in water and the more aqueous system.

In order to determine whether excess hydride is necessary for reduction, 10 mmol of 1-hexene was oxymercurated in a 1:1 THF–water (10 ml each) solvent system with 10 mmol of mercuric acetate. After 10 min, 10 ml of 3.0 *M* sodium hydroxide was added followed by various amounts of 0.5 *M* sodium borohydride in 3.0 *M* sodium hydroxide. The results (% excess H^-, % yield 2-hexanol: 10, 88; 50, 86; 100, 92) are essentially the same in all cases.

Another factor which may influence the yield is the temperature at which reduction takes place. Both styrene and 1-hexene were oxymercurated and base was added. The basic solutions were then either heated or cooled and borohydride solution (0.5 *M* sodium borohydride in 3.0 *M* sodium hydroxide, 100% excess) was added. The temperature was controlled during the addition. The yield of 2-hexanol varied between 88 and 95% with no trend observable. The results with styrene (Table IV) also show that the temperature of reduction is unimportant.

TABLE IV
EFFECT OF REDUCTION TEMPERATURE ON THE YIELD OF 1-PHENYLETHANOL

Reduction temp, °C	Yield of alcohol, %[a]	Reduction temp, °C	Yield of alcohol, %[a]
55–60	87	15–17	91
50–53	90	2–5	87
30–35	90	−5–0	91
32–35	89		

[a] Glpc analysis.

Mercuric salts, other than mercuric acetate, have also been used in the oxymercuration reaction. Mercuric nitrate and mercuric trifluoroacetate were allowed to react with several olefins in order to determine whether the anion had any pronounced effect on the reaction.

We explored the effect of the nature of the mercuric salt on the yield, using mercuric acetate, trifluoroacetate, and nitrate and a standard group of representative olefins. The results indicated that there was no significant change in the maximum yield with these salts. However, the yield dropped much more sharply with time in the case of the nitrate and the trifluoroacetate, especially with the more highly substituted olefins.[18] These results persuaded us that mercuric acetate would be most generally useful; so we adopted it for this study of the reaction scope.

With the above results in mind we designed a standard procedure for the oxymercuration–demercuration of olefins which is remarkable in its simplicity and speed.

In a 100-ml flask, fitted with a magnetic stirrer, is placed 3.19 g (10.0 mmol) of mercuric acetate. To this is added 10.0 ml of water (in which the salt dissolves), followed by 10.0 ml of THF. Then 10.0 mmol of 1-hexene is added. The reaction mixture is stirred for 15 min at room temperature (approximately 25°) to complete the oxymercuration stage. Then 10.0 ml of 3.0 *M* sodium hydroxide is added, followed by 10.0 ml of a solution of 0.50 *M* sodium borohydride in 3.0 *M* sodium hydroxide. Reduction of the mercurial is almost instantaneous. The mercury is allowed to settle. Sodium chloride or potassium carbonate is added to saturate the water layer. The upper layer of THF is separated—it contains an essentially quantitative yield of 2-hexanol, 94%.

We have encountered no serious difficulty in scaling the procedure up to runs on a preparative scale. However, it should be recognized that the reaction is exothermic, so that the rate of addition of base and basic hydride solutions should be controlled to maintain the temperature at approximately 25°.

As was pointed out previously the mercuric acetate originally dissolves in the water to give a clear solution. However, the addition of the THF forms a yellow precipitate. As the reaction proceeds, this coloration first becomes lighter and then the reaction mixture (usually) becomes colorless and clear (T_1), frequently in a matter of seconds, although in some cases, such as *trans*-4,4-dimethyl-2-pentene, longer periods are required. Although the oxymercuration reaction is not complete at this point, the disappearance of the yellow color provides an approximate indication of the time required. Usually we allowed the reaction to proceed for at least five to ten times the length of time required for the yellow color to vanish before initiating the reduction stage (T_2).

In considering the effect of olefin structure on the oxymercuration–demercuration reaction, it is advantageous to compare olefins with similar structural features. Consequently the data are presented individually for olefins of the following classes: I, monosubstituted terminal olefins, $RCH{=}CH_2$; II, disubstituted internal olefins, $RHC{=}CHR'$; III, disubstituted ter-

(18) A detailed study of this phenomenon is underway with J. T. Kurek and the results will be reported shortly.

minal olefins, $R_2C{=}CH_2$; IV, trisubstituted internal olefins, $R_2C{=}CHR$; V, tetrasubstituted internal olefins, $R_2C{=}CR_2$. Unless otherwise stated, all of the following reactions were run under the above standard conditions.

Terminal Olefins, RCH=CH₂.—The data for this series of olefins is given in Table V. The reaction is rapid and clean leading to a quantitative conversion to alcohol. The olefins react within 15 min to give greater than 90% of the Markovnikov alcohol. As has been mentioned previously, the higher molecular weight olefins react more rapidly when a less aqueous system is used.

TABLE V

OXYMERCURATION–DEMERCURATION OF TERMINAL OLEFINS, RCH=CH₂

Olefin	T_1, sec	T_2, hr	Product	Yield, %[a]
1-Pentene	15	0.25	2-Pentanol	93
		1.0		97
1-Hexene	45	0.25	2-Hexanol	94
		1.0		95
1-Dodecene[b]		0.25	2-Dodecanol	91
		1.0		91
1-Octadecene[c]		0.25	2-Octadecanol	86
		1.0		93
3,3-Dimethyl-1-butene	120	0.25	3,3-Dimethyl-2-butanol	86
		1.0		94
Styrene	30	0.25	1-Phenylethanol	91
		1.0		90

[a] Glpc analysis. [b] THF:H_2O = 2:1. [c] THF:H_2O = 3:1.

Oxymercuration is known to proceed in the Markovnikov sense, that is, by placing mercury on the carbon atom which originally held the larger number of hydrogen atoms. The apparent homogeneity of the isolated mercurials, coupled with chemical determination of the positions occupied by –OR and –HgX, form the original experimental basis for this observation. Recently Kiefer and Waters have determined the nmr spectra of a number of isolated mercurials and have stated that the "methoxymercuration of all unsymmetrical olefins (which they studied) took place cleanly in the Markovnikov sense."[19]

We subjected the reaction mixtures obtained from 1-hexene, 3,3-dimethyl-1-butene, and 2-methyl-1-butene to careful glpc examination in order to determine quantitatively the purity of the Markovnikov alcohol formed in the reaction.

The product from 1-hexene revealed the presence of 0.5% of 1-hexanol on oxymercuration under our standard conditions. This alcohol was identified by its retention time. Addition of authentic 1-hexanol to the reaction mixture caused an appropriate increase in the size of the peak of this minor component.

Examination of the reaction mixture from 3,3-dimethyl-1-butene revealed a peak corresponding to 3% of the anti-Markovnikov alcohol product. Isolation of this material by preparative gas chromatography and comparison of its ir and nmr spectra and glpc retention time with those of an authentic sample identified it as 3,3-dimethyl-1-butanol.

There was less than 0.1% 2-methyl-1-butanol in the reaction mixture from 2-methyl-1-butene.

Thus the oxymercuration–demercuration reaction provides an extremely simple and quantitative method for Markovnikov hydration of monosubstituted olefins to give almost exclusively the desired isomer.

An examination of the glpc trace of the reaction mixture from oxymercuration of 3,3-dimethyl-1-butene failed to reveal the presence of any 2,3-dimethyl-2-butanol (<0.2%) which would be the product expected if the intermediate secondary carbonium ion were to rearrange to the tertiary ion. This lack of rearrangement is an important characteristic of the oxymercuration reaction.[11]

Disubstituted Internal Olefins, RCH=CHR′.—The yield of alcohols and percentage of 2-ols have been tabulated in Table VI. Here again the yield of alcohol from the various olefins is quantitative except for the somewhat lower yields for the propenylbenzenes.

This series of olefins brings out several important aspects of the oxymercuration–demercuration reaction. The first of these is that *cis* isomers react more rapidly than the corresponding *trans* olefins. This observation is based on the disappearance of the yellow precipitate (T_1). As partial confirmation of this is the observation that the yield of alcohol from *trans*-4,4-dimethyl-2-pentene is 52% after 6 hr, while the yield of alcohol from the corresponding *cis* isomer has reached 95% in 4 hr. This phenomenon has been noted previously,[20] and in one case its use in determining the configuration of isomeric olefins has been suggested.[20c]

The second aspect of this reaction that is evident from these data is the dramatic variation in rate of reaction with increased branching in the olefin. Taft has reported that the rate of hydration of olefins of the type $RC(CH_3){=}CH_2$ varies only slightly as R is changed from methyl (relative rate = 1.0) to ethyl (relative rate = 1.25) to *t*-butyl (relative rate = 1.0).[21] In contrast T_1 varies by a factor of about 500 from methyl to *t*-butyl in the oxymercuration of *trans*-$RCH{=}CHCH_3$. It thus appears that a rather large steric effect is operable in the oxymercuration–demercuration reaction. (The effect is smaller in the *cis* isomers.)

The distribution of the alcoholic OH group in the product between the two olefinic carbon atoms of the starting material also demonstrates the high susceptibility of this reaction to steric factors. The incoming OH group becomes attached preferentially to the least hindered carbon atom. The large preference of the OH group for the 2 position with increased inaccessibility of the 3 position is obvious from comparison of the relative amounts of 2-ol and 3-ol in either the *cis*- or the *trans*-4-substituted 2-pentenes (Table VI).

Herz and Gonzalez have recently reported that oxymercuration–demercuration of 5α-cholest-2-ene gives a 30:70 mixture of 2β- and 3α-cholestanols.[22]

Epoxidation of several 5α-cholest-2-enes has resulted in the formation of the α-epoxides, indicating that the α side is the least hindered side for such reactions.[23]

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TABLE VI

DISUBSTITUTED INTERNAL OLEFINS, RCH=CHR'

Olefin	Registry no.	T_1	T_2, hr	Yield of alcohol, %[a]	Isomers, % 2-ol[b]	Isomers, % 3-ol[c]
cis-2-Pentene	627-20-3	25 sec	0.25	93	64	36
trans-2-Pentene	646-04-8	50 sec	0.25	91	56	44
cis-4-Methyl-2-pentene	691-38-3	3 min	1.0	97	91	9
trans-4-Methyl-2-pentene	674-76-0	10 min	3.5	99	82	18
cis-4,4-Dimethyl-2-pentene	762-63-0	7 min	3.5	95	98	2
trans-4,4-Dimethyl-2-pentene	690-08-4	8 hr	16.0	91	95	5
cis-Propenylbenzene	166-90-5	45 min	24.0	77	88	12
trans-Propenylbenzene	873-66-5	5.5 hr	24.0	55	30[d]	70
Cyclopentene	142-29-0	20 sec	1.0	91		
Cyclohexene	110-83-8	55 sec	0.25	96		
Cyclooctene	931-88-4	2 hr	3.0	88		

[a] Total yield of both positional isomers. [b] $RCH_2CHOHCH_3$. [c] $RCHOHCH_2CH_3$. [d] Value at 15 min, yield approximately 5%. The per cent 2-ol gradually approaches that of the *cis* isomer.

TABLE VII

DISUBSTITUTED TERMINAL OLEFINS, $R_2C=CH_2$

Olefin	Registry no.	T_1	T_2, hr	Product	Yield, %[a]
2-Methyl-1-butene	563-46-2	10 sec	0.08	2-Methyl-1-butanol	90
			1.0		92
2,4,4-Trimethyl-1-pentene	107-39-1	3 min	0.30	2,4,4-Trimethyl-2-pentanol	87
Methylenecyclohexane	1192-37-6	10 sec	0.08	1-Methylcyclohexanol	99
α-Methylstyrene	98-83-9	45 sec	0.17	2-Phenyl-2-propanol	95

[a] Glpc analysis.

Attack by the mercuric salt (or ion) on the least hindered α side, followed by *trans* attack by water (diaxial addition) on the more hindered β side, would lead to the minor product. *trans*-Diaxial addition, initiated by mercury attack from the more hindered side, would give rise to the major product. Thus the product is apparently determined by the relative ease of attack by water on the intermediate.

The susceptibility of the oxymercuration–demercuration reaction to steric factors is indicated by these rather limited data.

Disubstituted Terminal Olefins, $R_2C=CH_2$.—These olefins can be oxymercurated to give quantitative yields of the corresponding tertiary alcohols in very short reaction times (Table VII). As mentioned previously, the reaction mixture from 2-methyl-1-butene was examined in order to determine the amount of anti-Markovnikov addition, but no 2-methyl-1-butanol could be detected.

Oxymercuration of 2,4,4-trimethyl-1-pentene proceeds smoothly to give an 87% yield of 2,4,4-trimethyl-2-pentanol in 18 min. Longer reaction times have a deleterious effect on the yield of alcohol. When the reaction is allowed to proceed for 8 hr, the yield of alcohol drops to 25%. After 24 hr, the yield is only 1% (Figure 1). In contrast the yield of 2-methyl-2-butanol from 2-methyl-2-butene remains at about 93% over a 24-hr period (Figure 1). Here again it appears as if a highly branched substituent has a profound effect on the course of the reaction.

Although the yield of alcohol in the case of 2,4,4-trimethyl-1-pentene is satisfactory, we have found that it is difficult to reproduce the maximum yield. This is primarily due to the sharp maximum and the heterogeneous nature of the initial stages of the reaction. This causes the reaction to proceed somewhat faster in some cases than in others, and makes it difficult to establish exactly when the maximum yield of alcohol has been attained.

In order to circumvent this difficulty, the reaction was run using 20 ml of THF for every 10 mmol of olefin (2:1 THF:H_2O). The maximum yield obtainable under these conditions was 71%. Increasing the amount of water to 20 ml/10 mmol of olefin (1:2 THF:H_2O) merely displaced the curve toward longer reaction times. The maximum yield (87%) was the same but the time required to obtain this maximum was slightly longer (~20 min).

The reaction was also carried out at 0–5°. In this case the yield of alcohol remained constant at the maximum (~87%) for a relatively long time (Figure 1). It thus appears as if the problem of undesirable side reactions (at least of the type observed here) for highly substituted olefins can be circumvented by running the reaction at somewhat lower temperatures.

Trisubstituted Internal Olefins, $R_2C=CHR$.—A wide variation in reactivity is displayed by olefins in this class, ranging from rapid and quantitative reaction for 2-methyl-1-butene to relative inertness for 1-phenylcyclopentene (Table VIII).

The behavior of 2-methyl-2-butene and 2,4,4-trimethyl-2-pentene is quite similar to that of the isomeric 1-olefins. The yield of 2-methyl-2-butanol from 2-methyl-2-butene reaches a maximum of 94% within 15 min and maintains this value for at least 24 hr (Figure 2). The yield of alcohol from 2,4,4-trimethyl-2-pentene reaches a maximum of about 70% in 0.5 hr and then decreases rapidly to 38% in 8 hr and 4% in 24 hr (Figure 2). When this olefin was oxymercurated at 0°, the yield of alcohol increased to 86% and was stable for several hours (Figure 2).

1-Phenylcyclopentene and 1-phenylcyclohexene are unreactive under our reaction conditions. Thus at the end of 4 hr the olefin is recovered unchanged.

TABLE VIII

TRISUBSTITUTED INTERNAL OLEFINS, $R_2C{=}CHR$

Olefin	Registry no.	T_1	T_2, hr	Product	Yield, %[a]
2-Methyl-2-butene	513-35-9	20 sec	0.25	2-Methyl-2-butanol	94
2,4,4-Trimethyl-2-pentene	107-40-4	30 min	1.5	2,4,4-Trimethyl-2-pentanol	72 (86)[b]
1-Methylcyclopentene	693-89-0	20 sec	0.10	1-Methylcyclopentanol	93
1-Methylcyclohexene	591-49-1	10 sec	0.08	1-Methylcyclohexanol	100
1-Phenylcyclopentene	825-54-7	>4 hr	4.0	1-Phenylcyclopentanol	0
1-Phenylcyclohexene	771-98-2	>4 hr	4.0	1-Phenylcyclohexanol	0

[a] Glpc analysis. [b] Reaction at 0°.

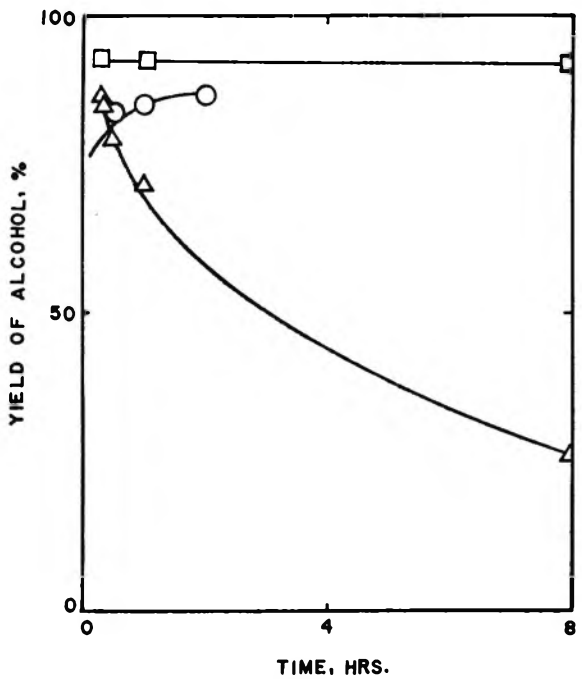

Figure 1.—Comparison of the yield of alcohol in the oxymercuration of 2,4,4-trimethyl-1-pentene at room temperature, Δ, and at 0°, O, with that of 2-methyl-1-butene, □.

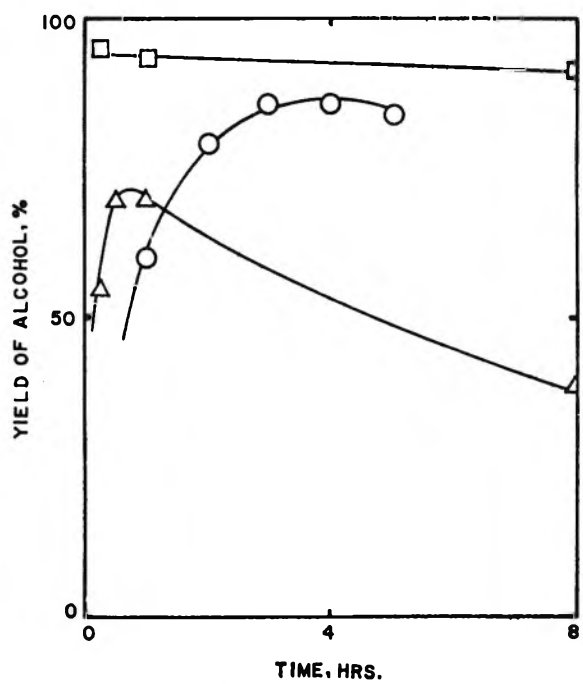

Figure 2.—Comparison of the oxymercuration of 2,4,4-trimethyl-2-pentene at room temperature, Δ, and at 0°, O, with that of 2-methyl-2-butene, □.

When 1 mmol of mercuric acetate was allowed to react with 10 mmol of 1-phenylcyclohexene for 8 hr (10 ml of water, 10 ml of THF), the yellow color did not disappear indicating that the reaction had proceeded less than 10% in this length of time.

Tetrasubstituted Internal Olefins, $R_2C{=}CR_2$.—The only olefin of this class which we studied was 2,3-dimethyl-2-butene. Under our conditions 2,3-dimethyl-2-butanol is obtained in 85% yield in 15 min. As with the diisobutylenes previously discussed, the yield of alcohol decreases rapidly with time. After 8 hr, only 5% of the alcohol remains (Figure 3). Reaction at 0° slows the secondary reactions and increases the yield of alcohol slightly in this case also (Figure 3).

Investigation of the reaction mixture at the end of 8 hr clarified the course of the secondary reactions. The majority of the mercury was present as mercurous acetate, which precipitated from solution during the course of the reaction, and which was identified by comparison of its decomposition point (~270°) and ir spectra with that of an authentic sample of mercurous acetate.

There was 45% of the olefin and 5% of the tertiary alcohol. The products of oxidation were 2,3-dimethyl-2,3-butanediol (18%) and 3,3-dimethyl-2-butanone (17%). The latter compound was partially reduced under the reaction conditions to 3,3-dimethyl-2-butanol. The diol and the secondary alcohol were isolated and identified by comparison of their retention times and ir and nmr spectra with those of authentic compounds and with published spectra.

The products indicate that oxidation takes place by ionization of the tertiary mercurial to the tertiary carbonium ion,[24] which then rearranges to the ketone or reacts with water to form the diol.

Conclusion

The oxymercuration–demercuration sequence has been used to prepare the Markovnikov alcohol from a wide variety of olefins. It involves a simple procedure, easily applied. It appears to be of wide scope, applicable to a large number of structural types. 1-Phenylcyclopentene and -cyclohexene were the only olefins found to be unreactive. High molecular weight olefins react better in a less aqueous solvent, *i.e.*, one in which the proportion of THF has been increased. Highly branched (*e.g.*, diisobutylene-1 or -2) or highly sub-

(24) F. R. Jensen and R. J. Ouellette, *J. Amer. Chem. Soc.*, **85**, 363, 367 (1963).

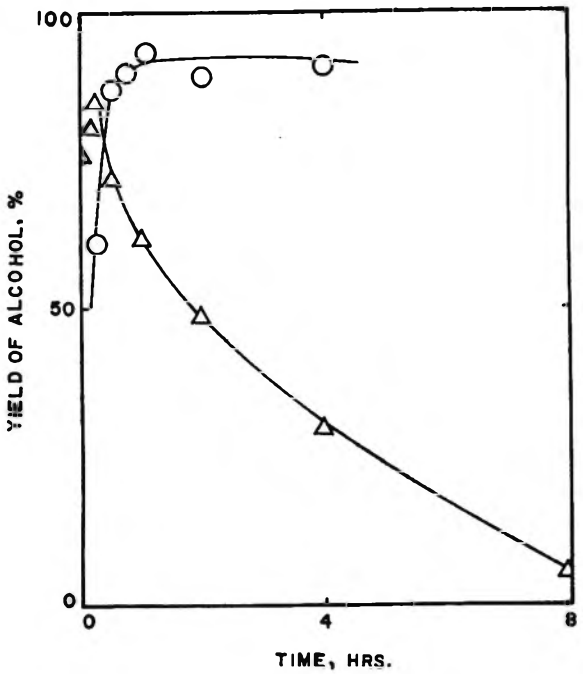

Figure 3.—Comparison of the oxymercuration of 2,3-dimethyl-2-butene at room temperature, Δ, and at 0°, O.

stituted (*e.g.*, tetramethylethylene) olefins are best run at 0° to minimize side reactions.

Experimental Section

Materials.—All olefins used were commercially available and were used as obtained unless glpc or index of refraction data indicated inpurities.

Mercuric acetate (Mallinckrodt Chemical Works), mercuric nitrate and mercuric oxide (J. T. Baker Chemical Co.), trifluoro acetic acid (3M Co.), sodium borohydride (Metal Hydrides, Inc.), and tetrahydrofuran (Fischer Scientific Co.) were used without further purification. Mercuric trifluoroacetate was prepared by a variation[6] of the method of Shearer and Wright.[25]

Oxymercuration Procedure.—The general procedure and various modifications have been discussed in appropriate places in the text.

Analysis.—The alcohol products were identified by comparison of gas chromatographic retention times with those of authentic samples of the alcohols. In several cases the products were isolated and compared with the known alcohols. Quantitative determinations were made by adding a suitable standard to the reaction mixture after reduction by borohydride. Calculations of yields were then made on the basis of relative thermal conductivities of standard and product as determined by integration of peaks obtained from a solution of standard and authentic alcohol. Analyses were carried out on either an F & M Model 300 chromatograph or a Perkin-Elmer Model 226 chromatograph. Integrations were obtained by using either a disk chart integrator or a Keuffel and Esser Co. planimeter.

Registry No.—1-Pentene, 109-67-1; 1-hexene, 592-41-6; 1-dodecene, 112-41-4; 1-octadecene, 112-88-9; 3,3-dimethyl-1-butene, 558-37-2; styrene, 100-42-5; 2,3-dimethyl-2-butene, 563-79-1.

(25) D. A. Shearer and G. F. Wright, *Can. J. Chem.*, **33**, 1002 (1955).

Factors Affecting Base-Induced Rearrangements of α-Chloro-α,α-diphenylacetamides

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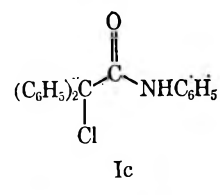
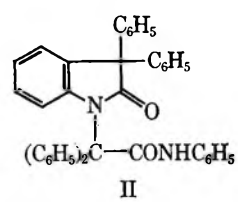
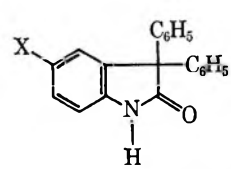
Effects of substituents and conditions on product distribution in reactions of N-substituted α-chloro-α,α-diphenylacetamides (Ia–Ie) with sodium amide in liquid ammonia, with liquid ammonia, and with aqueous ammonia are described. In liquid ammonia, in the presence or in the absence of sodium amide, the reaction leads to a product mixture consisting of two types of rearrangement products: (a) substituted ureas (VIIa and VIIb) and N-substituted α-amino amides (VIb–VIe), and (b) one displacement product (Va–Ve). These results are discussed in terms of a multistage process involving the intermediacy of a reactive α-lactam which undergoes two modes of ring opening. Formation of corresponding oxindoles (III) from the reactions of I in aqueous ammonia is also discussed.

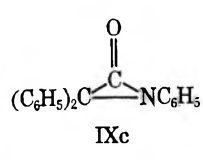
Although α-chloro-α,α-diphenylacetanilide (Ic) was known since 1912,[1] a more systematic study of its chemistry has been realized only in the last decade. This development was induced by the endeavors aimed at synthesizing 1,3,3-triphenylaziridinone (α-lactam, IXc) from the reaction of Ic with strong bases.[2]

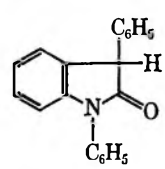
The reaction of Ic with sodium hydride in boiling benzene[3] was shown to yield a mixture of oxindole derivatives of structures II (predominant),[4] III (minor), and Ic (in minute quantities).[5] The formation of


Ic


II


IIIa, X = H
b, X = OCH$_3$


IXc


IV

IXc as an intermediate was invoked to explain the Ic → II conversion.[4]

(1) H. Klinger and G. Nickell, *Justus Liebigs Ann. Chem.*, **390**, 365 (1912).

(2) Endeavors aimed at synthesizing IXc from the reaction of Ic with strong base were unfruitful: (a) I. Lengyel and J. C. Sheehan, *Angew. Chem., Int. Ed. Engl.*, **7**, 25 (1968); (b) J. C. Sheehan and J. H. Beeson, *J. Amer. Chem. Soc.*, **89**, 366 (1967). (c) However, H. E. Baumgarten, R. D. Clark, L. S. Endres, L. D. Hagemeier, and V. J. Elia [*Tetrahedron Lett.*, 5033 (1967)] have reported that "1-*t*-butyl-3,3-diphenylaziridinone does not appear to be appreciably less stable thermally than the monophenyl α-lactam, 1-*t*-butyl-3-phenylaziridinone [H. E. Baumgarten, *et al.*, *J. Amer. Chem. Soc.*, **85**, 3303 (1963)], although it is *much more reactive chemically.*"

(3) S. Sarel and H. Leader, *ibid.*, **82**, 4752 (1960).

(4) S. Sarel, J. T. Klug, E. Breuer, and F. D'Angeli, *Tetrahedron Lett.*, 1553 (1964).

(5) J. C. Sheehan and S. W. Frankenfeld, *J. Amer. Chem. Soc.*, **83**, 4792 (1961).

TABLE I
REACTIONS OF α-CHLORO-α,α-DIPHENYLACETAMIDES (Ia–Ie) WITH SODIUM AMIDE

$$\text{I} \xrightarrow{\text{NaNH}_2\text{–NH}_3} \text{V} + \text{VI} + \text{VII}$$

Substrate	R in I	Product distribution, % V	VI	VII
Ia	H	20	...	70
Ib	C_6H_{11}	4	≤1	88
Ic	C_6H_5	18	19	49
Id	p-$C_6H_4OCH_3$	43	19	28
Ie	p-$C_6H_4SO_2N(CH_3)_2$	57	28	5

TABLE II
REACTION OF α-CHLORO-α,α-DIPHENYLACETAMIDES WITH AMMONIA UNDER VARIOUS CONDITIONS

$(C_6H_5)_2CCONHR$ | Cl I	NH_3	Temp, °C	$NaNH_2$	$(C_6H_5)_2$-CCONHR | OH V	$(C_6H_5)_2$-CCONHR | NH_2 VI	$(C_6H_5)_2$-CCONH$_2$ | NHR VI	$(C_6H_5)_2$-CHNCONH$_2$ | R VII
R = H	Liquid	−33	+	...	20	...	70
R = H	Liquid	Room	−	...	20	...	79
R = H	Aqueous	Room	−	20	75	...	...
R = C_6H_5	Liquid	−33	+	...	19	18	49
R = C_6H_5	Liquid	Room	−	...	32	29	39
R = C_6H_5	Aqueous	Room	−	35	25	...	...
R = C_6H_{11}	Liquid	−33	+	...	4	1	88
R = C_6H_{11}	Liquid	Room	−	...	72	4	16
R = C_6H_{11}	Aqueous	Room	−	28	60	...	...

Of particular interest is the reaction of Ic with sodium amide in liquid ammonia, which was shown to provide a mixture of three isomeric products, two of which (VIc and VIIc) must arise from rearrangement reactions, whereas the third one (Vc) seemingly constitutes a displacement product.[6]

The present study was aimed at clarifying the base-induced rearrangement of α-halo amides into the corresponding α-amino amides (VI) and urea derivatives (VII), and factors influencing the extent of these reactions. The substrates (Ia–Ie) were prepared by allowing α-chloro-α,α-diphenylacetylchloride to react with a slight excess of the appropriate amine at low temperature.

The α-chloro amides listed above were exposed to the action of (a) sodium amide in liquid ammonia at −33°, (b) liquid ammonia at 25° (autoclave), and (c) concentrated aqueous ammonia at room temperatures.

The products from the reactions in sodium amide and in liquid ammonia invariably comprised the respective displacement product V and the two rearrangement products VI and VII. Separation of V, VI, and VII was achieved by fractional crystallization and/or by column chromatography.

Distribution of products resulting from the reactions of Ia–Ie with sodium amide in liquid ammonia are given in Table I. Table II summarizes the results obtained in the reactions of Ia–Ic with liquid ammonia under various conditions. The results obtained from the reactions of Ia–Ie in aqueous ammonia are assembled in Table III. Tables IV–VIII summarize the melting points, ir spectra, and analysis of products appearing in Tables I–III.

TABLE III
REACTIONS OF α-CHLORO-α,α-DIPHENYLACETAMIDES (Ia–Ie) WITH AQUEOUS AMMONIA

$$\text{I} \xrightarrow{\text{NH}_4\text{OH}} \text{V} + \text{XX} + \text{oxindole (III)}$$

Substrate	Product distribution, % V	XX	Oxindole
Ia	75	20	...
Ib	60	28	...
Ic	25	35	10 (IIIa)
Id	25	17	52 (IIIb)
Ie	29	63	...

$$(C_6H_5)_2C(Cl)CONHR \longrightarrow (C_6H_5)_2C(NH_2)CONHR + (C_6H_5)_2C(NHR)CONH_2 + (C_6H_5)_2CH{-}N(R){-}CONH_2$$

I → V + VI + VII

a, R = H
b, R = C_6H_{11}
c, R = C_6H_5
d, R = p-$C_6H_4OCH_3$
e, R = p-$C_4H_4SO_2N(CH_3)_2$

Structural assignments were based on ir, nmr, and mass spectral determinations, and in some cases also by comparison with specimens obtained from independent syntheses.

The 1700–1500-cm^{-1} region in the ir spectra was proved to be of analytical interest. From the location of the amide I and amide II absorption bands in the spectra,[7] it was possible to characterize the type of the amide (V or VI). Thus, secondary amide V shows very strong absorption at 1530 cm^{-1}, owing to the bending vibration of the N–H (amide II band), whereas similar absorption for the primary amide VI occurs at 1600 cm^{-1}.

Mass spectra were shown to be an extremely valuable and reliable tool in the deduction of the structures of the isomeric α-amino amides. In analogy to esters of α-amino acids,[8] we found that in all α-amino amides the most abundant fragments are ions resulting from α cleavage, as depicted below.

$$(C_6H_5)_2C(NR_3R_4)CONR_1R_2 \longrightarrow [(C_6H_5)_2C{=}NR_3R_4]^+ + R_1R_2$$

m/e 180

(6) S. Sarel, F. D'Angeli, J. T. Klug, and A. Taube, *Israel J. Chem.*, **2**, 167 (1964).

(7) L. J. Bellamy, "Infrared Spectra of Complex Molecules," Methuen, London, 1958.

(8) K. Biemann, J. Seibl, and F. Gapp, *J. Amer. Chem. Soc.*, **83**, 3795 (1961).

TABLE IV

PHYSICAL AND ANALYTICAL DATA OF α-CHLORO-α,α-DIPHENYLACETAMIDES

$(C_6H_5)_2CCONHR$
|
Cl

I

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}					
			C	H	N	C	H	N						
Ia	H	115	68.28	4.92	5.71	68.21	4.91	5.66	3450		1680	1670	1590	
Ib	C_6H_{11}	89–90	73.27	6.76	4.27	73.54	6.91	4.33	3450		1667			1530
Ic	C_6H_5	88–89	79.20	5.61	4.62	78.94	5.45	4.39	3370	3340	1675			1530
Id	p-$C_6H_4OCH_3$	103–105	71.69	5.12	3.98	71.41	5.05	4.12	3440	3290	1690	1615		1530
Ie	p-$C_6H_4SO_2N(CH_3)_2$	155–156	61.61	4.89	6.53	61.91	5.07	6.72				1660	1580	1530

TABLE V

PHYSICAL AND ANALYTICAL DATA OF α-HYDROXY-α,α-DIPHENYLACETAMIDES

$(C_6H_5)_2CCONHR$
|
OH

XX

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}					
			C	H	N	C	H	N						
XXa	H	154–155	73.99	5.77	6.11	73.98	5.66	6.10	3450	3400	1680	1590	1550	
XXb	C_6H_{11}	151–152	77.64	7.49	4.53	77.73	7.51	4.58	3320		1667	1665		1530
XXc	C_6H_5	177–178	79.20	5.61	4.62	78.94	5.45	4.39	3370	3340	1675			1530
XXd	p-$C_6H_4OCH_3$	183–184	75.65	5.74	4.20	76.02	5.93	4.71	3370	3340	1710	1590		1530
XXe	p-$C_6H_4SO_2N(CH_3)_2$	198–199	64.38	5.40	6.83	64.38	5.65	7.28	3420	3340	1700			1530

TABLE VI

PHYSICAL AND ANALYTICAL DATA OF α-AMINO-α,α-DIPHENYLACETAMIDES

$(C_6H_5)_2CCONHR$
|
NH_2

V

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}				
			C	H	N	C	H	N					
Va	H	150–151	74.31	6.24	12.38	74.40	6.16	12.30	3400	3390	1675	1660	
Vb	C_6H_{11}	122–123	77.88	7.84	9.08	77.54	8.06	9.48	3340		1665	1640	1520
Vc	C_6H_5	145–146	79.44	6.00	9.27	80.47	6.27	9.34	3370		1650	1600	1530
Vd	p-$C_6H_4OCH_3$	188	75.88	6.07	8.43	75.57	6.08	8.55	3400		1680	1600	1525
Ve	p-$C_6H_4SO_2N(CH_3)_2$	193–194	64.53	5.66	10.26	64.49	5.69	10.67	3400		1690	1620	1520

TABLE VII

PHYSICAL AND ANALYTICAL DATA OF α-AMINO-α,α-DIPHENYLACETAMIDES

$(C_6H_5)_2CCONH_2$
|
NHR

VI

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}				
			C	H	N	C	H	N					
VIb	C_6H_{11}	158–160	77.88	7.84	9.08	77.39	7.80	9.33	3470	3360	1680	1660	1600
VIc	C_6H_5	183–184	79.44	6.00	9.27	80.56	6.24	8.77	3480	3360	1680		1600
VId	p-$C_6H_4OCH_3$	213–214	75.88	6.07	8.43	76.32	6.56	8.70	3410	3320	1670	1640	
VIe	p-$C_6H_4SO_2N(CH_3)_2$	227–228	64.53	6.66	10.26	64.24	6.10	10.58	3420	3325	1690	1620	

TABLE VIII

PHYSICAL AND ANALYTICAL DATA OF SOME SUBSTITUTED UREAS

$(C_6H_5)_2CHNCONH_2$
|
R

VII

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}					
			C	H	N	C	H	N						
VIIa	H	145–146	74.31	6.24	12.38	74.42	6.20	12.42	3448	3268		1678	1613	1563
VIIb	C_6H_{11}	167–168	77.88	7.84	9.08	77.62	8.00	9.30	3450	3320		1655	1590	1580
VIIc	C_6H_5	170–171	79.44	6.00	9.27	79.64	5.85	9.31	3460	3320	3140	1670	1610	1590
VIId	p-$C_6H_4OCH_3$	177–178	75.88	6.07	8.43	76.15	6.10	8.90	3460	3320		1670	1640	
VIIe	p-$C_6H_4SO_2N(CH_3)_2$	216–217	64.53	5.66	10.26	64.61	5.85	10.27	3420	3320	3160	1670	1605	1590

Thus, by determining the *m/e* value of M − (CONR$_1$R$_2$), one can infer the nature of the substituents on the α nitrogen. Abundances of the most significant ions of the amino amides and the urea derivatives have been reported.[9]

We observed that N-aryl-α-amino amides of structures $(C_6H_5)_2C(NHAr)CONH_2$ and $(C_6H_5)_2C(NH_2)CONHAr$ lend themselves to facile acid hydrolysis[10] to the corresponding α-hydroxy amides (XX). This was advantageously utilized for characterization purposes throughout.[11] Whereas the hydrolysis of the more basic α-amino anilides V could be effected smoothly in aqueous media, the hydrolysis of the α-anilino amides VI is best achieved in 85% alcoholic solution.

$$\underset{\text{Vc–Ve}}{(C_6H_5)_2CCONHAr(NH_2)} \xrightarrow[H_2O,\ HCl]{\text{fast}} \underset{\text{XXc–XXe}}{(C_6H_5)_2CCONHAr(OH)} + NH_3$$

$$Ia + ArNH_2 \longrightarrow \underset{\text{VIc–VIe}}{(C_6H_5)_2CCONH_2(NHAr)} \xrightarrow[EtOH,\ HCl]{\text{slow}} \underset{\text{XXa}}{(C_6H_5)_2CCONH_2(OH)} + ArNH_2$$

In addition, the α-N-arylamides VIc–VIe were independently synthesized by treating α-chloro-α,α-diphenylacetamide (Ia) with respective aromatic amine.[5]

Structural assignments of substituted ureas VII were derived from their pyrolysis into cyanuric acid and the corresponding N-benzhydrylamine derivative[12] (VII → XXI), which were also obtained by way of alkaline hydrolysis of VII (VII → IX).

$$\underset{\text{XXI}}{(C_6H_5)_2CHNHR} \xleftarrow{\text{pyrolysis}} \text{VII} \longrightarrow \underset{\text{XXI}}{(C_6H_5)_2CHNHR}$$

These amines (XXI) were characterized by comparison with specimens produced independently from the reaction of benzhydrylbromide with the appropriate amine.

We noticed that substituted benzhydryl ureas of structure VII lend themselves easily and selectively to acid hydrolysis, engendering benzhydrol and the respective monosubstituted urea XXII. We took advantage of this reaction for further characterization of the urea derivatives VII.

$$\text{VII} \xrightarrow[H_2O]{H^+} (C_6H_5)_2CHOH + \underset{\text{XXII}}{RNHCONH_2}$$

From Table I it can be seen that the effect of substitution on the amido nitrogen in the substrates is reflected most significantly by the product distribution. Thus the percentage of the corresponding urea derivatives decreases in the order VIIb > VIIa > VIIc > VIId ≫ VIIe. On the other hand, formation of the unrearranged α-amino amide increases in the same order, *viz.*, Vb < Va ∼ Vc < Vd < Ve. The effect of substitution on the formation of the rearranged α-amino amide VI is not so dramatic in the case of the aryl series VIc–VId as in the case with VIb, which is formed in less than 1% yield. This suggests that in the sodium amide catalyzed reactions the I → VI rearrangements are much less sensitive to polar effects of substitution than the I → VII rearrangements. The displacement reaction I → V, likewise, is highly susceptible to polar characteristics of the substituent on nitrogen in I.

From the data assembled in Table II it is clear that the rearrangement of I to VI and VII is effected by ammonia alone,[13] although it requires somewhat higher temperatures than in the presence of sodium amide. Whereas in the cases of Ia and Ic, yields of the rearrangement products VI and VII compare with the sodium amide reactions, yields of VIb and VIIb from the reaction of the least acidic amide, Ib, drop dramatically if sodium amide is excluded from the reacting system.

In view of the above we deemed it of interest to investigate the behavior of Ia–Ie in concentrated aqueous ammonia at room temperature. The results are summarized in Table III. It can be seen from this table that the rearrangements of the types I → VI and I → VII were not observed. The displacement reactions, forming α-hydroxy acetamides (I → XX) and α-amino acetamides (I → V), are predominant. The XX to V ratio is greater than one, where R = aryl, and considerably smaller than one in the case where R = H or C_6H_5. The most striking difference between these two groups of substrates (with the exclusion of the electron-deficient Ie) is noted in the product composition. Compounds Ic and Id give rise to oxindole derivatives, IIIa and 5-methoxy-3,3-diphenyloxindole (IIIb), in 10 and 51.4% yields, respectively.

5-Methoxy-3,3-diphenyloxindole (IIIb) was conveniently obtained, in good yield, also by thermal dehydrochlorination (250°) of Id. This is in parallel to the thermal conversion of Ic into IIIa. Klinger[1] assigned a hexaphenyldiketopiperazine structure to the product similarly obtained by heating Ic (neat) at 250°. This assignment is proved to be erroneous, and the correct structure of the product is IIIa.

It is most likely that the I → VI and I → VII rearrangements proceed *via* a common intermediate of an α-lactam structure. Possible mechanisms for the reaction are described in Charts I–III.

Mechanisms 1–3 depict the I → VI + VII rearrangement as a multistage process, involving an initial 1,3-elimination stage to form a true α-lactam, followed by nucleophilic attack on carbonyl carbon to give X, which in turn undergoes ring opening to give VI and VII. Mechanistically, they represent three different routes for the elimination step.

Mechanism 1 is an intramolecular SN2-type displacement which could also be labeled as a SNi process. The best analogy appears to be the Ramberg–Backlund reaction of α-bromo sulfone.[14]

(9) (a) E. Breuer, S. Sarel, A. Taube, and J. Sharvit, *Israel J. Chem.*, **6**, 777 (1968); (b) A. Taube, Doctoral Dissertation, The Hebrew University of Jerusalem, 1968.

(10) *Cf.* (a) R. N. Lacey, *J. Chem. Soc.*, 1933 (1960); (b) A. G. Davis and J. Kenyon, *Quart. Rev.* (London), **9**, 203 (1955).

(11) J. T. Klug, Doctoral Dissertation, The Hebrew University of Jerusalem, 1965.

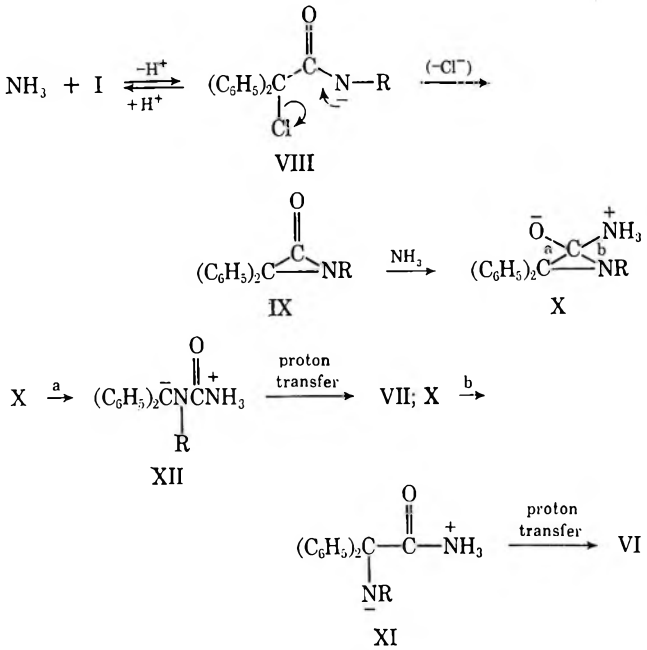
(12) (a) T. Mukaiyama, M. Tokiazawa, and H. Takei, *J. Org. Chem.*, **27**, 803 (1962); (b) T. Mukaiyama, H. Takei, and Y. Koma, *Bull. Chem. Soc. Jap.*, **36**, 95 (1963), and references cited therein.

(13) *Cf.* S. Sarel, A. Taube, and E. Breuer, *Chem. Ind.* (London), 1095 (1967). See also ref 2c.

(14) L. Ramberg and B. Backlund, *Ark. Kemi Mineral Geol.*, **13A**, No. 27 (1940). See F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968), and references cited therein.

CHART I

MECHANISM 1



solvolysis to form a carbonium ion XVIII, which gives an α-lactam species XIX. This mechanism, although it appears to be likely in displacement reactions occurring in aqueous ammonia (I → V + XX), seems unlikely in the sodium amide induced rearrangements, since it gives no role to the base.

The attachment of ammonia to α-lactam carbonyl to form a dipolar adduct X is invoked to explain substituent effects in the sodium amide catalyzed rearrangement of I into VI and VII. Two modes of ring opening are envisaged for the ammonia adduct: (a) mode a, which pursues the route X → XII → VII; and (b) mode b, which follows the X → XI → VI route. The inductive effects of the substituents on nitrogen are expected to increase yields of urea derivatives in the order VIIb > VIIa > VIIc > VIId > VIIe (mode a), and likewise to decrease yields of VI (mode b), which was found to be the case.

It is not possible to estimate the yield of VIa from the reaction of Ia, since VIa is identical with Va, which results from a displacement reaction. From another study described in a following paper,[17] it is inferred that Va originates mainly from the Ia → X → XI → Va route.

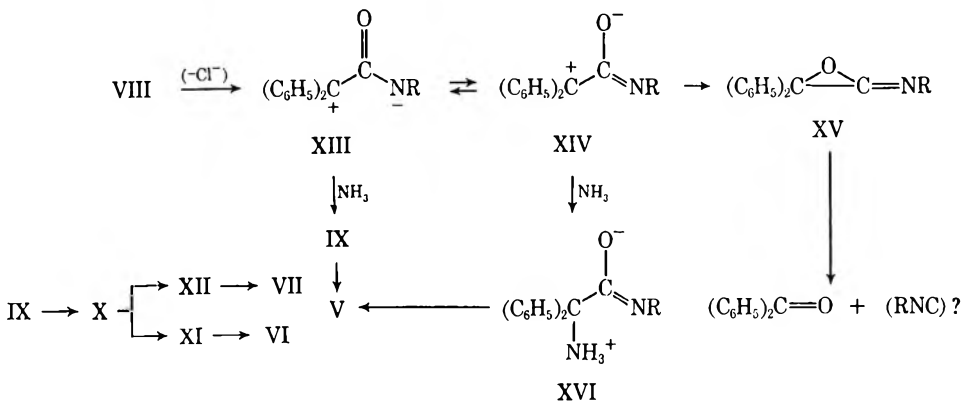
The low yield (15%) of VIIb from the reaction of Ib in the absence of sodium amide in liquid ammonia, compared with the yield (88%) from the sodium amide catalyzed reaction, is believed to be due to the low acidity of the amide group in Ib.

This amide (Ib) is the least acidic substrate, relative to Ia and Ic–Ie. It requires a stronger base for the 1,3-elimination stage (mechanisms 1–3) to form the α-lactam intermediate. As a consequence, the competing displacement reaction (Ib → Vb) *via* mechanism 4 becomes prominent.

Lack of rearrangement in the reaction of I in aqueous ammonia probably originates from the differences in basicities between liquid ammonia and aqueous ammonia. Most amides, having pK_a values of 14–34, will behave as neutral substances in aqueous ammonia but will exhibit acidic properties in liquid ammonia,[18]

CHART II

MECHANISM 2



In mechanism 2 considerable positive charge is developing at the α carbon atom as the chloride ion dissociates from the anion VIII to form dipolar ion XIII–XIV, believed to be invoked by π participation, transforming into a true α-lactam form or into the oxazirane form (XV). Formation of benzophenone in the reactions of Ia and Ib most likely arises from the fragmentation of the thermolabile XV.[2] This is in analogy to the mechanism of the Favorskii rearrangement of α-halo ketones.[15]

Mechanism 3 is a concerted 1,3 elimination giving an α-lactam intermediate. Although this possibility cannot be ruled out for our systems, no evidence in its favor could be found in the analogous Favorskii rearrangement.[15]

Mechanism 4 is based on the assumption that the role of the base is to establish an amide–imidol equilibrium,[16] and that the allylic system XVII undergoes

(15) F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *J. Amer. Chem. Soc.*, **91**, 2087 (1969), and references cited therein.

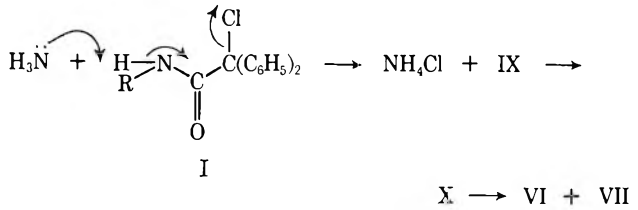
(16) The calculated value of ΔH for the amide → *imidol* change is +10 kcal/mol, compared with +18 kcal/mol obtained for the *keto* → *enol* change in ketones: G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1945, p 288–289.

(17) S. Sarel, A. Taube, and E. Breuer, forthcoming paper.

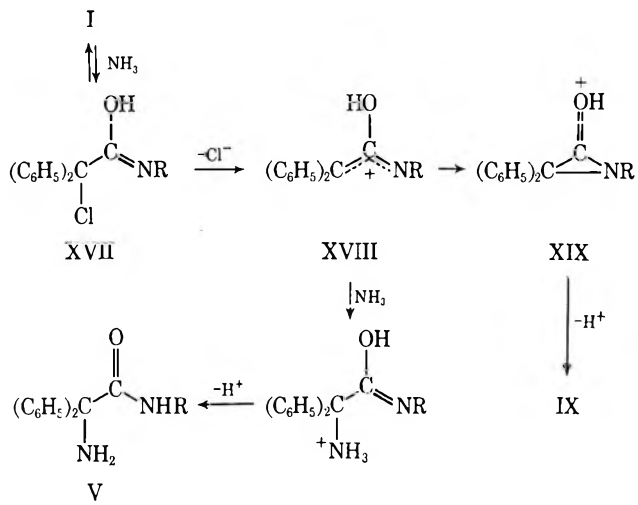
(18) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, New York, N. Y., 1963. See also R. C. Paul in "New Pathways in Inorganic Chemistry," E. A. V. Ebsworth, A. G. Maddock, and A. G. Sharpe, Ed., Cambridge University Press, New York, N. Y., 1968, p 233.

CHART III

MECHANISM 3

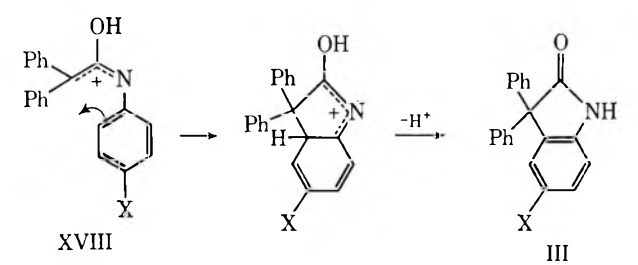


MECHANISM 4



the autoionization constant of which is *ca.* 10^{-32}. Aqueous ammonia is therefore too weak a base to play a role in 1,3-elimination reactions as formulated in mechanisms 1–3. However, mechanism 4 could be applied to explain the results summarized in Table III.

Formation of a carbonium ion of structure XVIII (mechanism 4) is invoked to explain the formation of 3,3-diphenyloxindoles (III) from the reactions of Ic and Id in aqueous ammonia. The reaction is viewed as an intramolecular cyclization process in which the electron-rich *p*-anisyl substituent contributes to the high yield (51%) of 5-methoxy-3,3-diphenyloxindole from the reaction of Id, compared with none in the case of Ie.



Experimental Section

All melting points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Column chromatography was carried out using Hopkin & Williams alkaline and neutral alumina.

N-Phenylbenzhydrylamine[19] was prepared in 63% yield from the reaction of phenylmagnesium bromide with N-phenylbenzalimine[20] in boiling toluene (18-hr reflux) and converted into its hydrochloride salt, mp 199°, by passing dry hydrogen chloride into an ethereal solution.

N-Cyclohexylbenzhydrylamine hydrochloride, mp 269–270°, was obtained in 50% yield from the addition of phenylmagnesium bromide to N-cyclohexylbenzalimine,[21] in a manner described above. The picrate melted at 185–187°.

N-(*p*-Anisyl)benzhydrylamine was prepared in 72% yield by treating benzhydryl bromide (10 mmol) with *p*-anisidine (20 mmol) in boiling benzene for 20 hr. The oily, crude product was chromatographed on an alumina column with benzene as eluent and finally isolated as its hydrochloride salt, mp 198–199° (lit.[22] mp 194°).

Anal. Calcd for $C_{20}H_{20}ClNO$: C, 73.7; H, 6.1; N, 4.3. Found: C, 73.6; N, 4.4.

N^4-(Benzhydryl)-N^1-dimethylsulfanylamide.—*p*-Aminobenzene-N,N-dimethylsulfonamide was obtained in 72% yield according to the literature,[23] mp 170–171° (prisms from ethanol).

The title compound was prepared in 63% yield by allowing a mixture of *p*-aminobenzene-N,N-dimethylsulfanylamide (9.5 mmol), benzhydryl bromide (10.5 mmol), and triethylamine (3 ml) in dry dioxane (50 ml) to stand at room temperature for 1 week. Colorless prisms were obtained from chloroform, mp 209–210°, ir (KBr) 3350 and 1580 cm^{-1}.

Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.8; H, 6.0; N, 7.7. Found: C, 69.1; H, 6.2; N, 7.7.

Cyclohexylurea, mp 205°, was prepared according to the literature.[24]

Preparation of α-Chloro-α,α-diphenylacetamides.—All N-substituted acetamides (Ia–Ie) were prepared by treating α-chloro-α,α-diphenylacetyl chloride[25] with 2 equiv of amine in dry ether.[1] Physical and analytical data are listed in Table IV.

Reaction of α-Chloro-α,α-diphenylacetamides with Sodium Amide in Liquid Ammonia.—α-Halo amides included in this study were similarly allowed to react with sodium amide in liquid ammonia. Physical and analytical data of the products obtained are given in Tables VI–VIII. The following procedure is representative.

A. Reaction of Ic with Sodium Amide in Liquid Ammonia.—To a mixture of sodium amide (0.5 g, 0.0128 mol) in dry liquid ammonia (70 ml), Ic (3.2 g, (0.01 mol) was added with stirring during 5 min. The ammonia was allowed then to evaporate and the residue was neutralized with ammonium chloride (0.5 g). The resulting mixture was treated first with cold dilute acid and then extracted with ether, leaving behind 1.47 g (49%) of VIIc, mp 170–171°. The nmr spectrum ($CDCl_3$) of VIIc exhibits a multiplet at τ 5.08 ($CONH_2$) and a multiplet centered at τ 2.85 (15 aromatic protons + benzhydrilic proton). Physical and analytical data for the corresponding compound are listed in Table VIII.

To the acidic filtrate, sodium carbonate was added and the alkaline precipitate was filtered and crystallized from ethanol, yielding 0.545 g (18.15%) of Vc, mp 145–146°. Physical and analytical data for corresponding compounds are listed in Table VI.

The ethereal extracts were concentrated and the residue was crystallized from benzene–petroleum ether, providing 0.56 g (18.5%) of VIc, mp 183–184°. Physical and analytical data for related compounds are listed in Table VII.

B. Reaction of Ib with Sodium Amide in Liquid Ammonia.—Reaction B was carried out as described above. The solid residue left after the evaporation of ammonia was crystallized from chloroform–ligroin, affording 88% VIIb, mp 167–168°. The nmr spectrum ($CDCl_3$) VIIb exhibits a singlet at τ 4.1 (one benzhydrilic proton), a multiplet at τ 5.5 ($CONH_2$), and a multiplet centered at τ 2.65 (aromatic protons).

The mother liquor was chromatographed on an alumina column (10 g) and eluted with petroleum ether. The first fraction contained benzophenone (4%), which was characterized as its 2,4-dinitrophenylhydrazone. The second fraction contained only a minute amount (less than 1%) of VIb, mp 158–160°, while the last fraction, eluted with benzene, contained Vb (4%), mp 113–114°.

(19) H. Gilman, J. E. Kirby, and C. R. Kinney, *J. Amer. Chem. Soc.*, **51**, 2252 (1929).

(20) L. A. Bigelow and H. Eatough, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1951, p 80.

(21) E. D. Bergmann and S. Pinchas, *Rec. Trav. Chim. Pays-Bas*, **71**, 161 (1952).

(22) P. Grammaticakis, *Compt. Rend.*, **210**, 716 (1940).

(23) E. L. Eliel and K. W. Nelson, *J. Org. Chem.*, **20**, 1657 (1955).

(24) O. Wallach, *Justus Liebigs Ann. Chem.*, **343**, 46 (1905).

(25) J. H. Bilman and P. H. Hidy, *J. Amer. Chem. Soc.*, **65**, 760 (1943).

Acid Hydrolysis of 1,1-Disubstituted Ureas. A. Hydrolysis of VIIc.—Compound VIIc (0.65 g, 2.15 mmol) was dissolved in a 35-ml solution of hydrochloric acid (3%) in ethanol (60%). The mixture was refluxed for 4 hr and then concentrated to half of its volume. Hydrochloric acid (12%, 25 ml) was added and the resulting solution was extracted with benzene. The organic layer was evaporated and the oily residue was distilled under diminished pressure to give benzhydrol (71%), bp 102–104° (0.4 mm).

Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.60; H, 6.72.

The acidic aqueous layer was rendered alkaline and the resulting solution was concentrated. The precipitate formed was filtered, giving 0.12 g (40%) of phenylurea, mp 147°. A mixture melting point with a sample prepared according to the literature[26] was not depressed.

B. Hydrolysis of VIIb, in a manner described above, yielded cyclohexylurea, mp 201–205°, and benzhydrol (73%).

Base Hydrolysis of 1,1-Disubstituted Ureas. A. Hydrolysis of VIIc.—A solution of VIIc (1.6 mmol) in 0.07 *M* 85% ethanolic potassium hydroxide (35 ml) was refluxed for 5 hr and then processed in the usual way. Crystalline N-phenylbenzhydrylamine, mp 170–171°, was isolated. Its hydrochloride had a melting point of 199°, showing identity with an authentic specimen.

B. Hydrolysis of VIIb in the manner described above yielded N-cyclohexylbenzhydrylamine, which was characterized as its hydrochloride, mp 269–270°, and its picrate, mp 186–187°.

Pyrolysis of 1,1-Disubstituted Ureas. A. Pyrolysis of VIIc.—Compound VIIc (0.6 g, 2 mmol) was heated to 250° for 10 min. The resulting melt was cooled and then extracted with acetone (20 ml). The insoluble solid was crystallized from water, yielding 0.065 g (75.5%) of cyanuric acid.

Anal. Calcd for $C_3H_3N_3O_3$: C, 27.91; H, 2.34; N, 32.56. Found: C, 28.08; H, 2.99; N, 32.64.

The acetone extract was evaporated, and N-phenylbenzhydrylamine (XXI) was isolated as the hydrochloric salt, mp 199°. A mixture melting point with a sample prepared as described was not depressed.

B. Pyrolysis of VIIb was carried out in the manner described above. From the pyrolysis of 1 g of VIIb, 0.13 g (95%) of cyanuric acid and 0.8 g (94.5%) of N-cyclohexylbenzhydrylamine (XXIb) were isolated. The latter was characterized as its hydrochloride and its picrate derivatives.

C. Pyrolysis of VIId.—From the pyrolysis of 0.5 g of VIId, cyanuric acid and 0.31 g of N-(*p*-anisyl)-benzhydrylamine were isolated. The latter was characterized as its hydrochloride, mp 198–199°.

D. Pyrolysis of VIIe.—The pyrolysis of VIIe similarly provided crystals (from chloroform) of N^1-dimethyl-N^4-benzhydrylsulfanylamide, mp 208–209°, identical in all respects with an authentic sample.

Hydrolysis of VIc into α-Hydroxy-α,α-diphenylacetamide (XXa).—Compound VIc (0.53 g, 1.75 mmol) was dissolved in a solution of hydrochloric acid (6%) in ethanol. The resulting mixture was refluxed for 2 hr, the solvents were evaporated, and the residue was extracted with chloroform. The dried chloroform extract was evaporated and the oily residue was crystallized from benzene–petroleum ether. α-Hydroxy-α,α-diphenylacetamide (XXa), 0.2 g (50%), was obtained, mp 152–154° (lit.[27] mp 154–155°). A mixture melting point with authentic sample prepared by the hydrolysis of Ia was not depressed.

Hydrolysis of VId and VIe.—The hydrolyses of VId and VIe were similarly carried out to give α-hydroxy-α,α-diphenylacetamide (XXa), mp 152–154°.

Acid Hydrolysis of V. A. Acid Hydrolysis of Vc into α-Hydroxy-α,α-diphenylacetanilide (XXc).—Compound Vc (0.3 g, 1 mmol) was dissolved in dilute hydrochloric acid (15 ml) and the solution was refluxed for 10 min. The precipitate formed was filtered, dried, and crystallized from benzene–petroleum ether, giving α-hydroxy-α,α-diphenyl acetanilide (XXc), mp 177–178°. A mixture melting point with a sample prepared by the hydrolysis of Ic was not depressed.

B. Hydrolysis of Vd and Ve.—In a similar manner, Vd and Ve were quantitatively hydrolyzed into the respective α-hydroxy derivatives XXd and XXe. Physical and analytical data are given in Table V.

Reaction of Ic with Liquid Ammonia at −33°.—To a 100-ml, three-necked flask equipped with a condenser suited for acetone–Dry Ice and a calcium chloride drying tube was introduced dry liquid ammonia (60 ml). Powdered Ic (3.21 g, 0.01 mol) was added in one portion and the reaction mixture was stirred for 10 hr. The ammonia was then allowed to evaporate and the residue was extracted with benzene. The benzene solution was washed with three 15-ml portions of water, dried over magnesium sulfate, concentrated, and chromatographed on alumina column (100 g). On elution with benzene, unchanged starting material was obtained in 8.5% yield, followed by XXc (91%), mp 177–178°. A mixture melting point with an authentic sample prepared by the hydrolysis of Ic was not depressed.

Reactions of α-Chloro-α,α-diphenylacetamides with Liquid Ammonia at Room Temperature.—Reactions of I with liquid ammonia at room temperature were carried out in an autoclave. The following procedure is representative. A mixture of Ic (3.21 g, 0.01 mol) in liquid ammonia (50 ml) contained in a sealed tube was vigorously agitated for 48 hr. Ammonia was then allowed to evaporate and the residue was extracted with benzene and chromatographed on an alumina column (100 g). Elution with 1:1 benzene–petroleum ether gave Vc, mp 142–145°. A mixture melting point with a sample obtained from the reaction of the same substrate with sodium amide was not depressed.

Further elution with benzene gave VIc (28%), mp 181–182°. A mixture melting point with product obtained from the sodium amide reaction was not depressed. The third fraction eluted by chloroform afforded VIIc, mp 170–171°, in 32.2% yield.

Reaction of α-Chloro-α,α-diphenylacetamides with Aqueous Ammonia.—A mixture of I (0.01 mol) in concentrated aqueous ammonia 20–23%, (50 ml) was magnetically stirred during 1 week at room temperature. The solid which was deposited was filtered, treated with dilute hydrochloric acid, and washed with water. The dried solid was then crystallized from benzene–petroleum ether and identified as the respective α-hydroxy-α,α-diphenylacetamide derivative. The acidic filtrate was rendered alkaline, and from it the corresponding α-amino-α,α-diphenylacetamide derivative was isolated by filtration or by extraction with benzene.

Reaction of Ic with Aqueous Ammonia.—Fractional crystallization of the solid obtained from the reaction of Ic with aqueous ammonia gave the following products: (a) α-hydroxy-α,α-diphenylacetanilide (XXc, 35%), mp 176–179°; (b) 3,3-diphenyloxindole (IIIa, 10%), mp 228–229° (lit.[5] mp 227–228°), ir (KBr) 3330, 1725, and 1680 cm^{-1}.

From the filtrate, α-amino-α,α-diphenylacetanilide (VIc, 25%), mp 145–146°, was isolated.

Thermal Conversion of Ic into 3,3-Diphenyloxindole (IIIa).—The reaction was carried out according to Klinger and Nickell.[1] Compound Ic (1 g) was heated gradually to 230° during 1 hr. Evolution of hydrogen chloride began at 150° and ceased at the end of the experiment. The cooled melt was crystallized from benzene, yielding colorless prisms (85%), of mp 226–228° (lit.[1] mp 225–226°). A mixture melting point with an authentic specimen of 3,3-diphenyloxindole (IIIa) was not depressed. Its ir spectrum was superimposable upon that of authentic IIIa.

The assigned hexaphenyldiketopiperazine structure[1] for this product was not substantiated by molecular weight determination.

Preparation of 3,3-Diphenyl-5-methoxyoxindole (IIIb).—Compound Id (0.5 g, 1.42 mmol) was heated to 250° for 5 min. Evolution of hydrogen chloride was observed. The melt was then cooled, benzene (10 ml) was added, and the resulting mixture was warmed on a water bath. The formed precipitate was filtered and crystallized from ethanol or acetone. 3,3-Diphenyl-5-methoxyoxindole, mp 259–260°, was obtained in a yield of 0.28 g (62.5%), ir (KBr) 3400, 3240, 1710, and 1670 cm^{-1}. The infrared spectrum was superimposable upon that of the product obtained from the reaction of the same substrate with aqueous ammonia.

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.98; H, 5.63; N, 4.60.

Registry No.—N-Phenylbenzhydrylamine hydrochloride, 2101-21-5; N-cyclohexylbenzhydrylamine

(26) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co. Ltd., London, 1961, p 644.

(27) H. Klinger and O. Standke, *Chem. Ber.*, **22**, 1214 (1889).

hydrochloride, 844-41-7; N-cyclohexylbenzhydrylamine picrate, 989-12-8; *p*-aminobenzene-N-N-dimethylsulfonamide, 1709-59-7; N-(benzhydryl)-N′-dimethylsulfanylamide, 23511-18-4; cyclohexylurea, 698-90-8; N-(*p*-anisyl)benzhydrylamine hydrochloride, 23511-20-8; 3,3-diphenyl-5-methoxyoxindole, 20367-84-4; Ia, 722-96-3; Ib, 797-73-9; Ic, 741-36-6; Id, 23522-81-8; Ie, 23522-82-9; Va, 15427-81-3; Vb, 23522-84-1; Vc, 741-37-7; Vd, 23522-86-3; Ve, 23522-87-4; VIb, 15779-18-7; VIc, 741-38-8; VId, 23522-90-9; VIe, 23522-91-0; VIIa, 724-18-5; VIIb, 741-68-4; VIIc, 741-69-5; VIId, 23568-88-9; VIIe, 23568-89-0; XXa, 4746-87-6; XXb, 17003-65-5; XXc, 5554-37-0; XXd, 20594-45-0; XXe, 23568-86-7.

The Mechanism of Tetralone Formation from the Acid-Catalyzed Reaction of 2-(N,N-Dimethylamino)-1,4-diphenyl-1,4-butanediol

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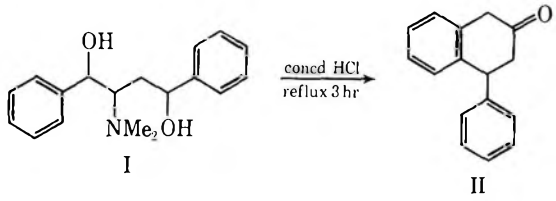
The mechanism of formation of 4-phenyl-2-tetralone from the reaction of 2-(N,N-dimethylamino)-1,4-diphenyl-1,4-butanediol with acid was investigated. A number of potential reaction intermediates were synthesized. These included 1,4-diphenyl-3-buten-2-one, 1,4-diphenyl-3-butene-1,2-diol, and 1,4-diphenyl-1,2,4-butanetriol. The first two of these compounds failed to give 4-phenyl-2-tetralone on treatment with hydrochloric acid. The triol did furnish 4-phenyl-2-tetralone in acid, but it was indirectly shown that the triol was not an intermediate in the reaction. A cyclic amino alcohol, 2-(N,N-dimethylamino)-4-phenyl-1-tetralol, afforded 4-phenyl-2-tetralone in high yield upon treatment with acid. Results of kinetic studies were consistent with intermediacy of the cyclic amino alcohol. Experimental data suggests a mechanism in which the cyclic amino alcohol undergoes dehydration to an enamine with subsequent hydrolysis to 4-phenyl-2-tetralone.

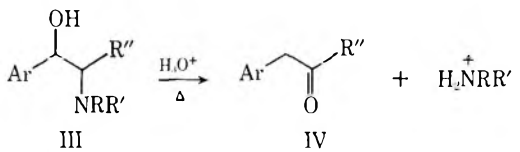
In a previous communication[2] we reported the acid-catalyzed conversion of 2-(N,N-dimethylamino)-1,4-diphenyl-1,4-butanediol (I) into 4-phenyl-2-tetralone (II). We now wish to report the results of



I II

experiments aimed at elucidating the mechanism of tetralone formation.

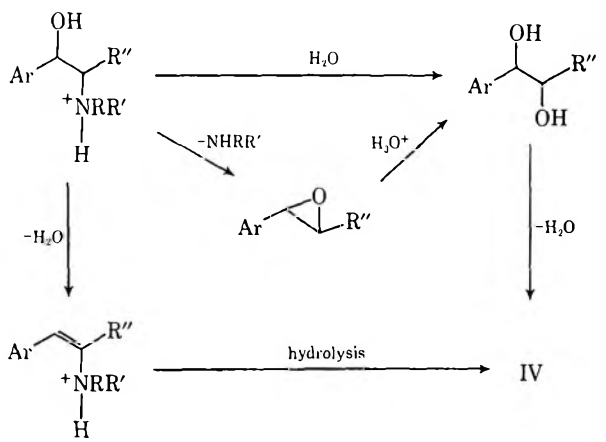
α-Aryl-β-amino alcohols are known to undergo cleavage to β-keto compounds upon treatment with strong mineral acids.[3-6] In these reactions R and R′



III IV

may be either hydrogen or alkyl, while R″ may be hydrogen, alkyl, or aryl. Because of their pharmaceutical activity, many amino alcohols related to III have been prepared; however, there are few studies dealing with the acid-catalyzed cleavage of these compounds. Among the mechanisms[3-5,7] which have been suggested to account for the cleavage, two proposals merit attention. These are outlined in Scheme I. One proposal involves conversion of the amino

SCHEME I



alcohol into a glycol, either *via* displacement of amine by neighboring hydroxyl and hydrolytic cleavage of the resulting epoxide or *via* direct displacement of amine by water.[3,4] The intermediate glycols are known to undergo acid-catalyzed dehydration to β-aryl ketones or aldehydes. In the cleavage of ephedrine derivatives with concentrated phosphoric acid the intermediate glycols were, indeed, isolated, but the mechanism of glycol formation has not been convincingly resolved.[3]

(1) To whom inquiries should be addressed.

(2) (a) S. A. Fine and R. L. Stern, *J. Org. Chem.*, **32**, 4132 (1967). (b) In ref 2a 4-phenyl-2-tetralone was synthesized independently *via* intramolecular Friedel–Crafts reaction of 1,4-diphenyl-3-buten-2-one. An unexpected by-product, not reported previously in this synthesis, was 2-naphthol, isolated by extracting the crude product with sodium hydroxide followed by acidification.

(3) F. Krönke and A. Schulze, *Chem. Ber.*, **75**, 1154 (1942).

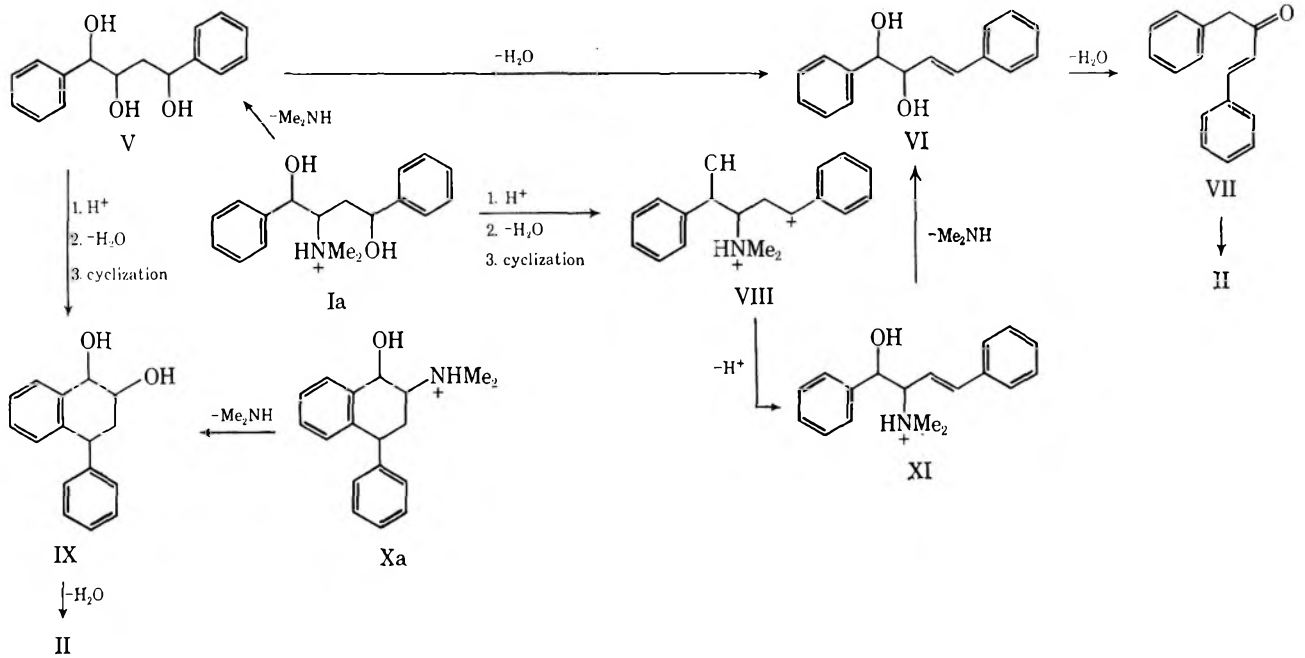
(4) H. Auterhoff and H. J. Roth, *Arch. Pharm.* (Weinheim), **289**, 470 (1956).

(5) P. T. Sou, *Bull. Fac. Sci. Univ. Franco-Chinoise*, **5**, 1 (1935); *Chem. Abstr.*, **30**, 4463 (1936).

(6) In ref 5 enamines were isolated when β-amino alcohols were treated with PCl_5.

(7) J. H. Fellman, *Nature*, **182**, 311 (1958).

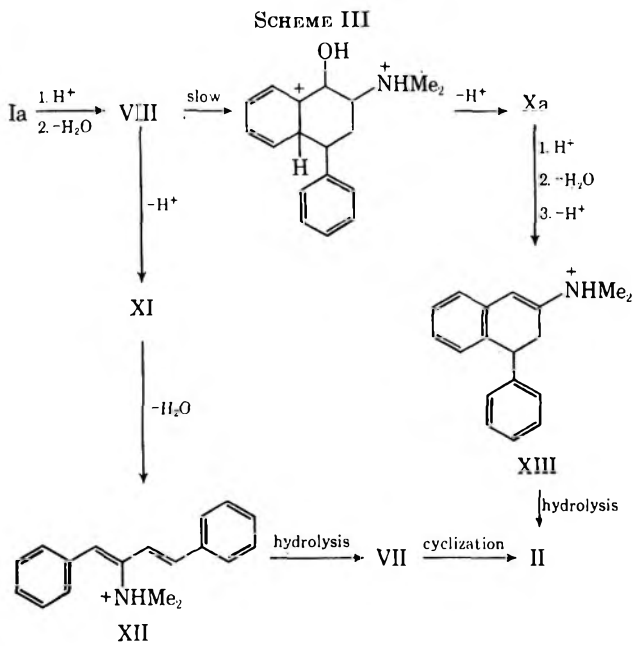
SCHEME II



An alternate mechanism involves dehydration of the amino alcohol to an enamine, which is subsequently hydrolyzed to an aldehyde or ketone.[3,5] However, convincing experimental evidence for the intermediacy of enamines is lacking.[6]

A priori, several pathways seem plausible for the acid-catalyzed conversion of aminodiol I into tetralone II. These may be conveniently arranged in sequences involving nucleophilic displacements at the carbon atom bearing the dimethylammonium moiety (Scheme II) or dehydration to enamines and subsequent hydrolysis to ketones (Scheme III). The diols VI and

SCHEME III



IX and triol V could be generated from the corresponding protonated amino alcohols *via* epoxidation and subsequent hydrolytic ring opening of the epoxides or by direct solvolytic displacement of the C-2 dimethylammonium group. The other reactions in Schemes II and III involve straightforward dehydrations and cyclizations. In order to reduce the number of mechanistic possibilities, synthesis of various intermediates was undertaken.

Results

The triol V was obtained as a mixture of stereoisomers upon borohydride reduction of the known hydroxydione XIV.[8] Likewise, the unsaturated diol VI was prepared from 1,4-diphenyl-3-butene-1,2-dione (XV); the latter was generated *via* selenium dioxide oxidation of 1,4-diphenyl-3-buten-2-one. The cyclic amino alcohol X was synthesized by reduction of the known amino ketone XVI[9] with lithium aluminum hydride. For comparison purposes the quaternary ammonium salt XVII was prepared by treatment of I with methyl iodide.

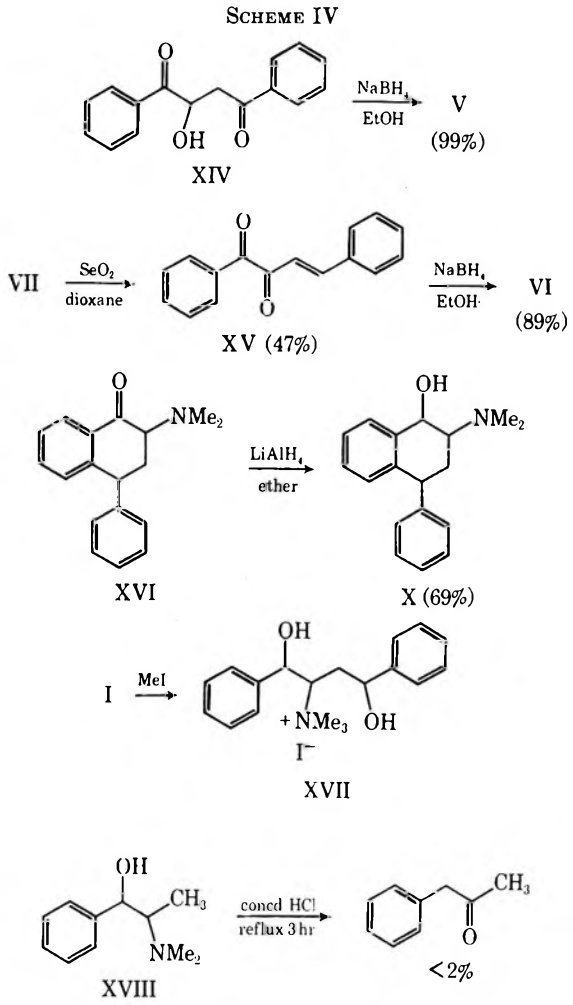
The intermediates were characterized by their elemental analyses, infrared spectra, and, in the case of VI, diagnostic chemical tests. The syntheses are summarized in Scheme IV.

Ketone VII was inert to refluxing concentrated hydrochloric acid; the unsaturated diol VI furnished a gum which, although unidentified, was shown *via* ir *not* to contain 4-phenyl-2-tetralone. The quaternary ammonium salt XVII afforded no 4-phenyl-2-tetralone. Both the triol V and the cyclic amino alcohol X afforded 4-phenyl-2-tetralone on treatment with hydrochloric acid. Infrared examination of the crude reaction product from V revealed the presence of a contaminant absorbing at 5.95 μ; no such contaminant was observed in the crude products from X and I.

In addition a model compound (XVIII), embodying the structural features of carbon atoms 1 and 2 in the aminodiol I, was subjected to concentrated hydrochloric acid and was found to be relatively unreactive.

(8) H. W. Dudley and S. Ochoa, *J. Chem. Soc.*, 625 (1933).
(9) S. Wawzonek and J. Kozikowski, *J. Amer. Chem. Soc.*, **76**, 1641 (1954).

SCHEME IV



In excess 6 *M* sulfuric acid at 110° the overall pseudo-first-order rate constant of tetralone formation from amino diol I was found to be $k_I = 8.56 \times 10^{-5}$ sec^{-1}. The activation energy for the reaction was determined by measuring the rates of the reaction at varying temperatures: $E_a = 26$ kcal/mol. The corresponding value determined for the entropy of activation was $\Delta S_0^{\ddagger} = -11$ eu. The rate constant of tetralone formation at 110° from the cyclic amino alcohol X is $k_X = 1.74 \times 10^{-4}$ sec^{-1}. Excellent straight-line plots were obtained in all runs except for slight convex curvature in the initial stages of the reactions.

Discussion

A priori, the unknown stereoisomeric composition of aminodiol I and of compounds V, VI, X, XVII, and XVIII would appear to curtail meaningful mechanistic conclusions. Fortunately, there is well-established evidence that optically active alcohols and β-amino alcohols in which the hydroxyl groups are benzylic undergo rapid acid-catalyzed racemization.[10-12] In these alcohols and, indeed, even in some simple *sec*-alkyl alcohols,[13] complete racemization was observed to occur prior to any detectable elimination. Hence the possible stereochemistry of the amino alcohols and polyols in the present case is unimportant, since *all* of their subsequent reactions occur in strongly acidic media.

The formation of tetralone from triol V necessitated a more definitive experiment in order to establish whether V was actually generated from I under the reaction conditions. Since trimethylamine is a weaker base than dimethylamine, the former should be a more effective leaving group than the latter. Hence, if nucleophilic displacement of the dimethylammonium group in aminodiol Ia can occur, the trimethylammonium substituent in XVII should be displaced with even greater facility. Because XVII is free to cyclize at C-4, the possibility of nucleophilic displacement at C-2 in Ia either before or after cyclization may be ruled out, thus excluding the intermediacy of V and IX.

The high-yield acid-catalyzed conversion of cyclic amino alcohol X into 4-phenyl-2-tetralone and the rates of tetralone formation from X and from I ($k_X/k_I \cong 2$ at 110°) are consistent with a mechanism of tetralone formation from I involving the intermediacy of X, although the data cannot be considered positive proof of such intermediacy. The fairly large negative entropy of activation in the sequence I → II suggests the formation of a cyclic transition state in the slow step. Hence, it seems likely that the rate-determining step involves intramolecular cyclization of the carbonium ion resulting from elimination of the protonated C-4 hydroxyl group in I (Scheme III).

The high reactivity of cyclic amino alcohol X toward acid is somewhat surprising in view of the much lower reactivity of XVIII. One factor which may contribute to this difference is that the fused aromatic ring of X has, in effect, an alkyl group *ortho* to the side chain bearing the benzylic hydroxyl group. The presence of this *ortho* substituent could inductively lower the activation energy for removal of the protonated hydroxyl group by providing added stabilization for the resulting carbonium ion. In addition, steric factors may contribute to the high reactivity of X toward acid. The formation of a stabilized benzylic carbonium ion demands coplanarity of the aromatic ring with the positively charged carbon atom and the two atoms directly attached to the latter. Examination of a molecular model of the carbonium ion derived from XVIII reveals serious steric repulsion between the large alkyl substituent and adjacent *ortho* hydrogen atom of the ring, thus rendering coplanarity difficult. Experimental support for this behavior is found in the solvolysis of α-phenylethyl chlorides, C_6H_5CHClR, in 80% aqueous ethanol, the relative rates of solvolysis decreasing rapidly with increasing size of R.[14] The geometry of the half-chair conformation of X is such that coplanarity of the aromatic ring and a developing benzylic carbonium ion is more easily achieved than in XVIII. Precedent for this hypothesis is found in the fact that 1-chlorotetralin undergoes ethanolysis at 25° more than 239 times faster than does 1-phenylethyl chloride.[15]

(10) H. Bretschneider, K. Biemann, W. Koller, and H. Sachsenmaier, *Monatsh. Chem.*, **81**, 31 (1950).
(11) L. G. Schroeter and T. Higuchi, *J. Amer. Pharm. Assoc.*, **47**, 426 (1958).
(12) E. Grunwald, A. Heller, and F. S. Klein, *J. Chem. Soc.*, 2604 (1957).
(13) D. V. Banthorpe, "Reaction Mechanisms in Organic Chemistry," Vol. II, Elsevier Publishing Co., New York, N. Y., 1963, p 145.
(14) G. Baddeley, J. Chadwick, and H. T. Taylor, *J. Chem. Soc.*, 2405 (1954).
(15) B. Baddeley and J. Chadwick, *ibid.*, 368 (1951).

Experimental Section[16]

1,4-Diphenyl-1,2,4-butanetriol (V).—A rapidly stirred suspension of 2-hydroxy-1,4-diphenyl-1,4-butanedione[8] (2.54 g, 10.0 mmol) in 95% ethanol (25 ml) was treated with sodium borohydride (378 mg, 10.0 mmol). The mixture became warm. After stirring for 0.5 hr the mixture was diluted with water and the ethanol was evaporated under reduced pressure, causing formation of a white, semisolid precipitate. The aqueous mixture was extracted four times with ether and the combined ether extracts were washed with water. Evaporation of solvent from the dried ether extract left a nearly colorless gum (2.56 g). Upon cooling overnight the gum became partially crystalline. Trituration with benzene containing a small amount of hexane followed by filtration gave a white, crystalline solid (858 mg). Recrystallization from benzene–cyclohexane (1:1) gave small, white plates (734 mg): mp 122–124°; ir 2.95 μ (s, broad, OH) and no carbonyl absorption.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.16; H, 7.07.

Evaporation of solvent from the benzene–hexane filtrate gave a colorless gum (1.58 g). Attempts to crystallize or distil the gum were unsuccessful: ir 2.95 μ and no carbonyl absorption.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.69; H, 7.22.

1,4-Diphenyl-3-butene-1,2-dione (XV).—A mixture of selenium dioxide (11.1 g, 0.100 mol), water (2 ml), and dioxane (70 ml) was warmed until homogeneous. 1,4-Diphenyl-3-buten-2-one (22 g, 0.10 mol) was added and the mixture was refluxed with stirring for 4 hr. The supernatant liquid was decanted from precipitated selenium and solvent was evaporated from the filtered solution under reduced pressure. The residual oil was distilled under vacuum, affording an orange oil, bp 150° (0.1 mm). Cooling the product for 2 days in a refrigerator caused it to solidify. Recrystallization from petroleum ether (bp 30–60°) gave 1,4-diphenyl-3-butene-1,2-dione (11 g, 47%) as yellow needles: mp 58.5–60° (lit.[17] mp 54–55°); ir 3.32 (aryl CH) and 6.05 μ (C=O) and no aliphatic CH.

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.39; H, 5.12. Found: C, 81.30; H, 5.18.

1,4-Diphenyl-3-butene-1,2-diol (VI).—A stirred mixture of 1,4-diphenyl-3-butene-1,2-dione (2.23 g, 9.45 mmol) and 95% ethanol (25 ml) was treated with sodium borohydride (360 mg, 9.52 mmol). An exothermic reaction occurred; stirring was continued for 0.5 hr. After the addition of water (75 ml) the solution was made slightly acidic by dropwise addition of 5% sulfuric acid and extracted three times with ether. Solvent was evaporated from the dried extract under reduced pressure, leaving a colorless gum (2.01 g). Recrystallization from benzene–petroleum ether (bp 60–110°) gave a white, crystalline solid, mp 60–90°. The compound decolorized a solution of bromine in carbon tetrachloride. Upon treatment with periodic acid followed by silver nitrate, the compound gave a white precipitate of silver iodate: ir 2.80 (sharp, OH), 2.95 (broad, OH), 3.34, and 3.48 μ (CH) and no carbonyl absorption.

Anal. Calcd for $C_{16}H_{16}O_2$: C, 80.01; H, 6.72. Found: C, 79.81; H, 6.55.

1,4-Diphenyl-1,4-butanediol-2-(N,N,N-trimethylammonium) Iodide (XVII).—A mixture of 2-(N,N-dimethylamino)-1,4-diphenyl-1,4-butanediol[2a] (2.0 g, 0.70 mmol) and methyl iodide (2.0 ml, 3.2 mmol) was heated gently on a steam bath for 10 min. After cooling to room temperature the mixture was triturated with acetone (15 ml) and filtered by suction, affording a white solid (1.43 g, 49%), mp 214–216°.

Anal. Calcd for $C_{19}H_{26}NO_2I$: C, 53.40; H, 6.13; N, 3.28; I, 29.69. Found: C, 53.22; H, 6.11; N, 3.03; I, 29.64.

4,4-Diphenyl-3-butenoic Acid.—The procedure of Borsche[18] was employed with a modified work-up. Diphenylacetaldehyde (50 g, 0.25 mol) was heated with malonic acid (30 g, 0.29 mol) and pyridine (50 g) for 3 hr on a steam bath with occasional swirling. The cooled reaction mixture was diluted with ice–water and acidified with 2 *N* sulfuric acid. The resulting mixture was extracted three times with ether. The combined ether extracts were washed twice with water and extracted three times with 10% sodium carbonate. Evaporation of solvent from the dried ether layer gave 17 g of recovered diphenylacetaldehyde (which could be recycled without purification in subsequent reactions with no reduction in yield).

The stirred basic layer was carefully acidified with 2 *N* sulfuric acid and the resulting white precipitate was collected, washed thoroughly with water, and dried. Recrystallization from petroleum ether (bp 60–110°) gave white crystals (25.1 g, 44%), mp 112–115° (lit.[18] mp 114–115°).

4,4-Diphenylbutyric Acid.—A solution of 4,4-diphenyl-3-butenoic acid (31.6 g, 0.133 mol) in absolute ethanol (200 ml) was hydrogenated over 10% palladium-on-charcoal catalyst (1 g) for 0.5 hr in a Parr apparatus. Filtration followed by evaporation of solvent under reduced pressure left a colorless oil which crystallized on standing. Recrystallization from petroleum ether (bp 60–110°)–benzene (10:1) gave white crystals (30.3 g, 0.126 mol, 95%), mp 103–106° (lit.[9] mp 103–106°).

2-(N,N-Dimethylamino)-4-phenyl-1-tetralol (X).—A solution of 2-(N,N-dimethylamino)-4-phenyl-1-tetralone (prepared *via* a sequence[9] starting with 4,4-diphenylbutyric acid) (8.6 g, 0.032 mol) was placed in the thimble of a Soxhlet extractor. A suspension of $LiAlH_4$ (1.00 g, 0.0264 mol) in anhydrous ether (100 ml) was refluxed so that the amino ketone was extracted into the mixture. After 19 hr the mixture was cooled to room temperature and excess $LiAlH_4$ was decomposed by dropwise addition of ethyl acetate (3 ml) in ether (5 ml) followed by slow, cautious addition of water (5 ml). The mixture was filtered with suction and solid material was washed thoroughly with ether. The organic filtrate was washed twice with water, twice with 10% Na_2CO_3, and again with water followed by drying ($MgSO_4$) and evaporation of solvent under reduced pressure, leaving a yellow-white solid (5.9 g, 69%). An analytical sample was prepared by two recrystallizations from *n*-butyl ether, giving white crystals: mp 130–146°; ir 2.87 μ (OH) and no carbonyl absorption.

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.85; H, 7.92; N, 5.24. Found: C, 81.06; H, 8.10; N, 5.17.

Attempted Reaction of 1,4-Diphenyl-3-buten-2-one (VII)[2a] with Hydrochloric Acid.—A mixture of the ketone (2 g, 9 mmol) and concentrated hydrochloric acid (50 ml) was refluxed for 18 hr with vigorous stirring. The cooled mixture was extracted with ether. Removal of solvent from the dried ether extract left a light yellow solid which had an ir spectrum identical with that of starting material.

Reaction of 1,4-Diphenyl-3-butene-1,2-diol (VI) with Hydrochloric Acid.—A mixture of the diol (524 mg, 2.18 mmol) and concentrated hydrochloric acid (25 ml) was refluxed for 3 hr. The cooled mixture was extracted three times with ether. The combined ether extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure, leaving an orange-brown oil (425 mg), ir 5.95 μ (conjugated C=O). There was no significant OH absorption and no absorption at 5.85 μ, the C=O wavelength in 4-phenyl-2-tetralone.[2a]

Reaction of 1,4-Diphenyl-1,2,4-butanetriol (V) with Hydrochloric Acid.—A mixture of the triol (11.2 g, 0.0433 mol, mixture of stereoisomers) and concentrated hydrochloric acid (300 ml) was refluxed for 3 hr. The cooled mixture was extracted three times with ether. The ether extract was washed with water, dried, and evaporated under reduced pressure, leaving an orange oil (11.0 g). Distillation under vacuum afforded a colorless oil (6.09 g): bp 124–130° (0.02 mm); ir 5.83 (C=O) and 5.95 μ (shoulder).

A portion of the product was reduced with sodium borohydride to a crystalline substance, mp 110–118°, which, after recrystallization from ethanol–water, was identified as 4-phenyl-2-tetralol by melting point (118–121°) and mixture melting point (119–122°) with an authentic sample.

Similar experimental results were obtained when either the crystalline isomer of the triol or the gum was employed separately.

Reaction of 1,4-Diphenyl-1,4-butanediol-2-(N,N,N-trimethylammonium) Iodide with Hydrochloric Acid.—A solution of the methiodide (1.43 g, 3.36 mmol) in concentrated hydrochloric acid (25 ml) was refluxed for 2 hr. The reaction mixture was cooled to room temperature and extracted with three portions of ether. The ether extract was washed with water, dried, and evaporated under reduced pressure, leaving a trace of tarry material.

(16) Melting points were taken on a Thomas–Hoover Unimelt apparatus and are uncorrected. Infrared spectra were determined in CCl_4 on a Beckman IR-8 instrument and were calibrated against the 6.23-μ peak of polystyrene. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(17) P. Ruggli, P. Weis, and H. Rupe, *Helv. Chim. Acta*, **29**, 1788 (1946).

(18) W. Borsche, *Justus Liebigs Ann. Chem.*, **526**, 1 (1936).

Benzene was added to the aqueous layer and water was removed by azeotropic distillation. A suspension of saltlike, white crystals, mp 163–178°, remained in the benzene.

Reaction of 2-(N,N-Dimethylamino)-1-phenylpropanol (XVIII)[19] with Hydrochloric Acid.—A solution of the amino alcohol (1.02 g, 5.69 mmol) in concentrated hydrochloric acid (30 ml) was refluxed 3 hr, cooled, diluted with water, and extracted three times with ether. The ether extract was washed with water and saturated sodium chloride solution and then dried, and the solvent was evaporated. The crude product (15 mg, 1.8%), a nearly colorless liquid, was identified as phenyl-2-propanone by comparison of ir spectra and by literature analogies[4,20] in which reaction of the same amino alcohol with phosphoric acid or sulfuric acid gave phenyl-2-propanone.

Reaction of 2-(N,N-Dimethylamino)-4-phenyl-1-tetralol with Hydrochloric Acid.—A solution of the cyclic amino alcohol (500 mg, 1.87 mmol) in concentrated hydrochloric acid was refluxed for 2 hr and then cooled on ice. The oil-containing mixture was extracted three times with ether and the combined ether extracts were washed twice with water. Drying followed by evaporation of ether under reduced pressure left a light yellow oil (365 mg, 88%). The ir spectrum of the crude product was superimposable with a spectrum of authentic 4-phenyl-2-tetralone.[2a] A portion of the product was reduced with sodium borohydride to 4-phenyl-2-tetralol, identical in every respect with an authentic sample.[2a]

Determination of Rates of Reaction of Amino Alcohols I and X with 6 *M* Sulfuric Acid.—A series of 50-ml flasks, each containing 6 *M* sulfuric acid (25.0 ml), were placed in an oil bath and the bath was heated slowly to the desired temperature. After 1 hr the amino alcohol was introduced into each flask and timing was begun with a stopwatch. During the reaction the flasks were swirled occasionally and the temperature of the oil bath was maintained within 0.5° of the desired value. At the end of the reaction, ice–water (15 ml) was added and the flask was immersed in ice–water immediately. The cooled reaction mixture was poured into a 60-ml separatory funnel and extracted with ether (two 20-ml portions followed by a 10-ml portion). The combined ether extracts were washed with water (10 ml) and saturated sodium chloride solution (10 ml) and dried ($MgSO_4$). The ether solution was filtered into a tared flask (filter paper and $MgSO_4$ were washed thoroughly with ether) and evaporated under reduced pressure, ultimately at 60–70°, until the weight of the flask remained constant. The results of the experiments and a representative run are tabulated in Tables I and II.

TABLE I

REPRESENTATIVE RUN. RAW KINETIC DATA FROM THE REACTION OF 2-(N,N-DIMETHYLAMINO)-4-PHENYL-1-TETRALOL (X) WITH 6 *M* H_2SO_4

Amino alcohol, mg	Temp, °C ± 0.5°	Reaction time, min	Isolated 4-phenyl-2-tetralone, mg
350	110	15	16.4
350	110	30	36.9
350	110	60	105.9
350	110	90	152.4
350	110	120	191.1

TABLE II

GRAPHICALLY DETERMINED PSEUDO-FIRST-ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE REACTIONS OF AMINO ALCOHOLS I AND X WITH 6 *M* H_2SO_4

Amino alcohol	Temp, °C	k, sec^{-1}
I	118	1.65×10^{-4}
I	110	8.56×10^{-5}
I	105	5.38×10^{-5}
X	110	1.74×10^{-4}

It follows that $(k_X/k_I)_{110°} = 2.03$. These data allow the graphical calculation[21] of activation parameters: $E_a = 26$ kcal/mol; $\Delta S^{\ddagger}_{\circ} = -11$ eu.

Registry No.—I, 14195-36-9; II, 14195-35-8; V, 19236-31-8; VI, 23885-33-8; X, 23885-34-9; XV, 23885-00-9; XVII, 23885-01-0.

(19) S. Sugasawa, T. Yamazaki, M. Kawanishi, and J. Iwao, *J. Pharm. Soc. Jap.*, **71**, 530 (1951).

(20) H. Takamatsu, *ibid.*, **76**, 1244 (1956).

(21) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1953, p 98 ff.

Titanium Chloride Catalyzed Addition of Aziridine to Ketones. A Route to N-Aziridinylenamines[1]

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Addition of aziridine to a series of cyclic ketones from C_5–C_8 in the presence of $TiCl_4$ and triethylamine produced 1,1-bis(aziridinyl)cycloalkanes, 1-N-aziridinylcycloalkenes, 1-N-(β-chloroethyl)cycloalkylimine, and 1-N-(β-aziridinylethyl)cycloalkylimine. The product ratio was dependent upon the ketone ring size and the ketone/$TiCl_4$ mole ratio. 1-N-Aziridinyl-1-cycloheptene (**10**) and 1-N-aziridinyl-1-cyclooctene were prepared in ~20% yield but no enamine could be isolated from cyclopentanone or cyclohexanone. 1,1-Bis(aziridinyl)cyclopentane (**2**) and cyclohexane (**3**) were synthesized for the first time; previously reported bisaziridinyl derivatives were shown to be 1-N-(β-aziridinylethyl)cycloalkylimines. 3-N-Aziridinyl-1-cyclohexene (**17**) was prepared by the addition of aziridine to 3-bromo-1-cyclohexene in the presence of potassium hydroxide; treatment of this derivative with strong bases at temperatures up to 150° failed to effect an isomerization to 1-N-aziridinyl-1-cyclohexene. All of the aziridine compounds decomposed at room temperature to yield low molecular weight polyaziridines. The structures of the derivatives were assigned on the basis of infrared, nmr, and mass spectral data.

Enamines are generally prepared by condensing aldehydes or ketones with secondary amines in aromatic solvents and removing the water evolved by azeotropic distillation. An alternate technique, which is more applicable to reaction mixtures containing low-boiling components, is to remove the water with an inorganic drying agent such as $CaCl_2$ or $MgSO_4$.[2] Recently White and Weingarten reported that titanium tetrachloride is a more effective drying agent for this reaction; it appears to enhance the reactivity of the carbonyl as well as scavenge the water.[3] We have utilized the activating influence of $TiCl_4$ to prepare enamines derived from aziridine; *i.e.*, we have prepared

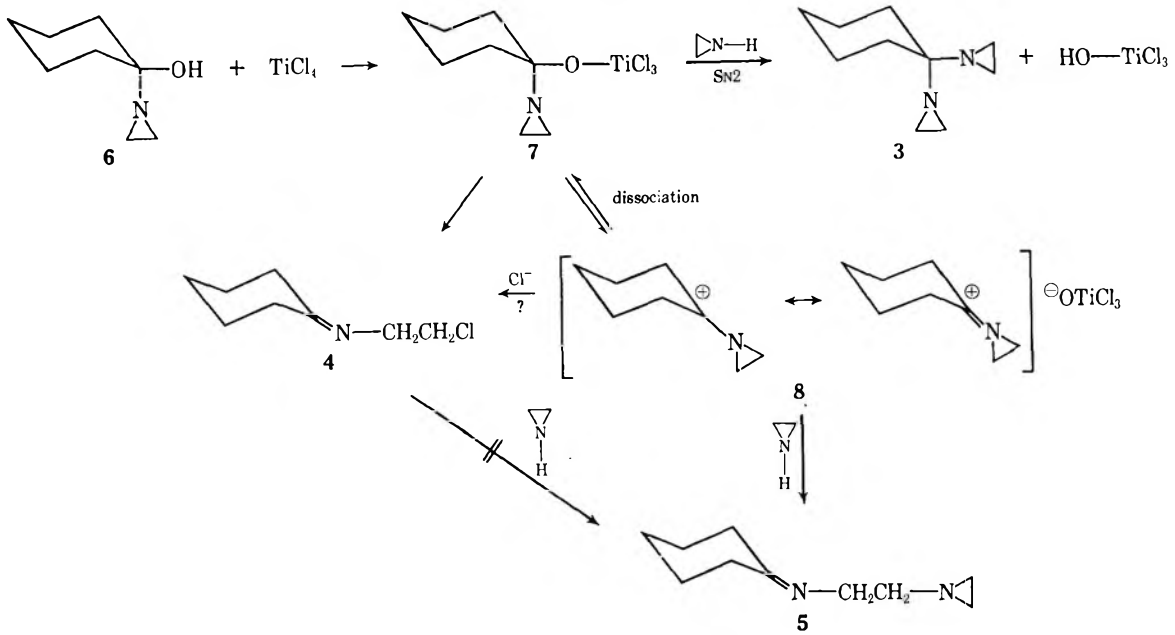
(1) Presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.

(2) L. W. Haynes, "Enamines," A. G. Cook, Ed., Marcel Dekker, Inc., New York, N. Y., 1969, Chapter 2.

(3) R. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).

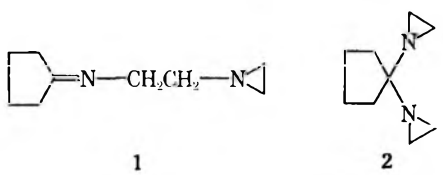
SCHEME I

PROPOSED MECHANISM FOR ADDITION OF AZIRIDINE TO CYCLOHEXANONE



1-N-aziridinylcycloheptene and -cyclooctene from the corresponding ketones. Although we could not isolate the enamines derived from cyclopentanone or cyclohexanone, this procedure enabled us to prepare 1,1-bis-(aziridinyl)cyclopentane and -cyclohexane.

The reaction of aziridine with cyclic ketones was initially studied by Dornow and Schacht.[4] They reported that cyclohexanone yielded 1-N-aziridinylcyclohexanol when the two reagents were combined at room temperature. After standing for several days, a mixture of cyclopentanone and aziridine afforded a low yield of a diadduct, which was postulated to be 1,1-bis(aziridinyl)cyclopentane on the basis of elemental analysis. The aminohydrin structure of the cyclohexanone derivative has been confirmed,[5] but the structure of the diadduct has not been challenged. We have prepared the diadduct according to the procedure of Dornow and Schacht and characterized the compound more completely. The nmr spectra exhibits a pair of triplets between δ 2.5 and 3.5 which is indicative of a β-(N-aziridinylethyl)cyclopentylimine (**1**) rather than the 1,1-bis(aziridinyl)cyclopentane (**2**)



initially proposed. Recently, the diadduct derived from benzaldehyde was assigned a β-(N-aziridinylethyl) structure similar to **1**.[6] Apparently the imine form of the diadduct is also favored when aromatic aldehydes are treated with excess aziridine. Thus, 1,1-bis(N-aziridinyl) derivatives of ketones have not been reported to date.

A few aziridinyl enamines have been prepared by addition of aziridine to activated acetylenes[7] or by displacement of an activated vinyl chloride.[8] Both of these procedures yield compounds with electron-withdrawing substituents conjugated with the double bond which reduce the nucleophilic character of the enamines. Since we are interested in the nucleophilicity of enamines, the preparation of unsubstituted aziridinyl enamines was undertaken.

Results and Discussion

The reaction of aziridine with cyclic ketones in the presence of titanium tetrachloride is complicated by the susceptibility of the aziridine ring to nucleophilic attack. We have found that at least three types of low-molecular-weight products as well as polymeric aziridine derivatives can be isolated from the reaction mixture. For example, treatment of cyclohexanone with excess aziridine yields 1,1-bis(aziridinyl)cyclohexane (**3**), N-(β-chloroethyl)cyclohexylimine (**4**), and N-(β-aziridinylethyl)cyclohexylimine (**5**) (see Scheme I). The nature of the products and the product distribution is dependent upon the ketone to $TiCl_4$ mole ratio, the ring size of the ketone, and the presence of an efficient acid acceptor.

The reaction of water with titanium tetrachloride produces hydrogen chloride which must be scavenged. In most cases, an excess of the amine component is added to neutralize the HCl. However, aziridine polymerizes in the presence of acids, and compound **4** is the only low-molecular-weight component formed when $TiCl_4$ is added to a mixture of cyclohexanone and aziridine. Obviously, neither aziridine nor polyethyl-

(4) A. Dornow and W. Schacht, *Chem. Ber.*, **82**, 464 (1949).

(5) R. G. Kostyanovoskii, *Dokl. Akad. Nauk SSSR*, **135**, 853 (1960); *Chem. Abstr.*, **55**, 12380a (1961). W. J. Rabourn and W. L. Howard, *J. Org. Chem.*, **27**, 1039 (1962). M. Lidaks and S. Hillers, *Latv. PSR Zinat. Akad. Vertis*, 99 (1961). *Chem. Abstr.*, **56**, 4706i (1962).

(6) Y. Oshiri, K. Yamamoto, and S. Komori, *Yuki Gosei Kagaku Kyokai Shi*, **24**, 945 (1966); *Chem. Abstr.*, **66**, 37706y (1967). M. Lidaks and S. Hillers, *Puti Sin. Izyskaniya Protivoopukholevykh Prep. Tr. Simp. Khim. Protivoopukholevykh Veshchestv, M*, 193 (1960); *Chem. Abstr.*, **58**, 4531c (1963).

(7) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965); A Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965); B. Giese and R. Huisgen, *ibid.*, 1889 (1967).

(8) H. W. Whitlock, Jr., and G. L. Smith, *ibid.*, 1389 (1965).

Table I

Reaction of Aziridine with Carbonyl Compounds

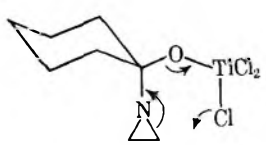
Run	Ketone	Mol of ketone/mol of $TiCl_4$	Product mixt bp, °C (mm)	Composition of mixt, %[a] Bis	Imine	Cl	Enamine	Wt of mixt/10 g of ketone	Yield[b] of bis adduct
1	Cyclohexanone	1/1	75–78 (6.2)	68	17.5	14.5	0	7.9	37
2	Cyclohexanone	1/0.5	91–100 (4.4)	44.4	55.5	0	0	4.9	13.3
3	Cyclohexanone	1/0.25	89–95 (3.0)	19	81	0	0	5.1	5.2
4	Cycloheptanone	1/1	90–95 (3.3)	29.2	0	37.2	33.6[c]	6.1	11
5	Cycloheptanone	1/0.5	88–94 (2.8)	0	23.6	24.2	52.2	2.2	
6	Cyclooctanone	1/1	76–111 (2.5)	0	0	56.8	43.2[d]	6.0	
7	3,3,5,5-Tetramethylcyclohexanone	1/1	100–106 (3.0)	24	0	61	17	1.6	3
8	Cyclopentanone	1/1	82–81 (5.3)	68	0	32	0	11.5	43
9	Benzaldehyde	1/1	100–110 (3.1)	23	34	43	0	8.2	11
10	Benzaldehyde[e]	1/1	103 (2.2)	0	0	100	0	2.3	
11	Benzaldehyde[f]	1/0	136 (9.5)	0	100	0	0	3.7	
12	Cyclopentanone[f]	1/0	85 (4.5)	0	100	0	0	0.15	

[a] The weight percentages were based on nmr analysis of volatile product mixture. [b] Based on ketone or benzaldehyde used. [c] A yield of 17% based on the ketone used. [d] A yield of 21.5% based on the ketone used. [e] No triethylamine present. [f] Aziridine and aldehyde or ketone stirred at room temperature without catalyst.

enimine is basic enough to completely scavenge the HCl. We have found that the addition of triethylamine to the initial ketone–aziridine mixture enables us to isolate a mixture of low-molecular-weight compounds as the major product, but the polymerization cannot be completely inhibited. We surveyed several other acid acceptors including pulverized sodium hydroxide, sodium carbonate, and pyridine; triethylamine was judged to be the most effective and most convenient.

The ketone to titanium tetrachloride mole ratio is an important factor in controlling the product distribution. The data in Table I show that equimolar ketone to $TiCl_4$ ratios (run 1) favor the formation of the bis-aziridinyl derivatives as well as the N-(β-chloroethyl)-imines. As the $TiCl_4$ concentration is decreased, the concentration of N-(β-aziridinylethyl)imines in the product mixture increases until they become the predominant compound of the distillate (run 3). There is a corresponding decrease in the overall yield of low-molecular-weight products as the ketone to $TiCl_4$ mole ratio is increased, so an equimolar stoichiometry of ketone and $TiCl_4$ is considered necessary for optimum yields of low-molecular-weight products.

Mechanism of Aziridine Addition.—The data in Table I can be rationalized by the following mechanism (Scheme I). When cyclohexanone is mixed with aziridine in benzene, 1-aziridinylcyclohexanol (**6**) precipitates. Addition of titanium tetrachloride converts the hydroxyl group to the more labile titanium alkoxide derivative **7**. A second mole of aziridine can then displace the titanate leaving group to produce 1,1-bis(aziridinyl)cyclohexane (**3**). High concentrations of $TiCl_4$ relative to the aminohydrin substrate will produce a minimum concentration of **7** and thus favor S_N2 displacement by aziridine. Since the formation of N-(β-chloroethyl)cyclohexylimine (**4**) is also enhanced by high $TiCl_4$ concentrations, a concerted displacement by a chloride atom attached to titanium is probably the predominant reaction pathway leading to **4**.[9] As a first approximation $[Cl^-]/[\text{aziridine}]$ in runs 1–3 remains constant; *i.e.*, in run 1, the formation of $ROTiCl_3$ (1 mol) produces 1 mol of $Et_3NH^+Cl^-$, and, in run 3, 1 mol of $Et_3{}^+NHCl^-$ would be produced if the formation of $(RO)_4Ti$ were sterically possible. Under these conditions one would expect the relative concentration of **4** to remain constant if free chloride attack on either intermediate **7** or **8** were the major source of **4**.



The titanate complex **7** could dissociate to produce a resonance-stabilized carbonium ion **8**. Nucleophilic attack on the activated aziridine ring of **8** by aziridine would yield **5**. The dissociation process would be favored sterically if more than one aminohydrin molecule were complexed with a molecule of titanium tetrachloride. This explains the increase in the carbonium ion derived product **5**, as the concentration of titanium tetrachloride is reduced. We have shown that **4** cannot be converted to **5** in the presence of excess aziridine under these reaction conditions. Carbonium ion **8** need not react solely at an aziridinyl carbon with concomitant cleavage of the ring. Attack by aziridine on the cyclohexyl ring may contribute to the formation of **3**. Chloride ions may also attack the tertiary carbonium ion, but reionization of the α-chloramine formed precludes the isolation of the product. Since enamines could be isolated from this reaction only when the more sterically hindered cycloheptanone and cyclooctanone substrates were employed, we believe that the carbonium ion intermediate is also required for enamine formation. This hypothesis is supported by the presence of an enamine component in the low molecular-weight products derived from 3,3,5,5-tetramethylcyclohexanone (run 7), which should exhibit a strong steric interaction between the titanate and aziridinyl substituents of the intermediate analogous to **7** and the two axial methyl groups in the 3 and 5 positions.

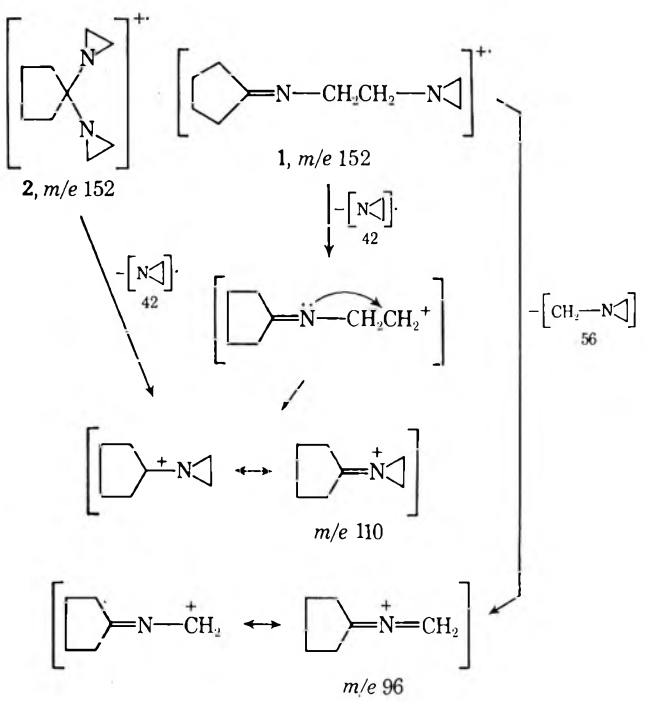
Spectral Characterization of the Aziridine Derivatives.—The structures were assigned to the products on the basis of infrared, nmr, and mass spectral data. The infrared spectra indicated the presence of the aziridine ring in compounds **3** and **5**; the sharp C–H stretch at 3080 cm^{-1} along with strong bands at 1260, 840, and 810 cm^{-1} are consistent with the values reported for

(9) We are grateful to a referee for suggesting this mechanism for the formation of **4**.

N-substituted aziridines.[10] Further, the imine derivatives **4** and **5** exhibited strong C=N stretching bands at 1660 and 1670 cm^{-1}, respectively.

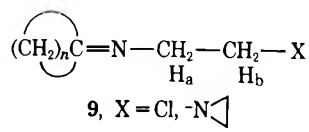
The mass spectra provide further support for the structure of **3** and **5**. Thus, bisaziridinyl derivatives fail to yield molecular ions, but the cracking patterns are similar to those observed for the N-(β-aziridinylethyl)imines. The major ions observed in the mass spectra of 1,1-bis(aziridinyl)cyclopentane (**2**) and N-(β-aziridinylethyl)cyclopentylimine (**1**) are assigned in Scheme II. The facile elimination of one aziridine

SCHEME II



ring from compound **2** would be expected for a bisaziridinyl derivative, for this produces a stabilized tertiary carbonium ion and probably relieves some steric strain. This effect is amplified in the cyclohexyl derivative. The principle peak in the spectrum of compound **3** occurs at *m/e* 124 (M − 42), and no larger ions can be observed. Compound **1** was prepared by the procedure of Dornow and Schacht to avoid contamination by the β-chloroethyl derivative. The spectrum of this compound clearly indicates the stability of the linear diadduct. The molecular ion as well as the ions produced by a stepwise loss of methylene groups are present in relatively high concentrations. A similar cracking pattern was observed for N-(β-aziridinylethyl)benzalimine. The mass spectrum of 1-N-aziridinylcycloheptene was consistent with the enamine structure. A strong molecular ion at *m/e* 137 confirms the stability of the monosubstituted cycloalkane. The cracking pattern indicated that initial decomposition occurred by loss of either ethylene or aziridine followed by a complex fragmentation, leading to a series of ions from 79 to 83 with similar intensities. These were probably generated by the loss of several hydrogen atoms from the cycloheptene ring. The principle peak was found at *m/e* 42, which corresponds to the aziridinyl cation.

The most conclusive evidence for the structure of the low-molecular-weight products was obtained from the nmr spectra. The aziridine rings in the bisaziridinyl derivatives **2** and **3** do not undergo rapid inversion; therefore, two signals corresponding to the *syn* (δ 1.12–1.32) and *anti* (δ 1.60–1.80) protons[11] are observed. The cycloalkane protons appear as a complex multiplet centering around δ 1.45. No absorptions above δ 1.10 or below δ 1.8 were observed. In contrast to the spectra of the bisaziridinyl derivatives, the spectra of both the N-(β-chloroethyl)imines and the N-(β-aziridinylethyl)imines exhibited complex multiplets below δ 1.8. These multiplets were assigned to the protons in the ethylene group bridging the cycloalkane and aziridine rings (**9**). By comparing the spectra of several similar derivatives, the low-field absorption (δ ~3.5–3.7) was assigned to H_a. The higher field absorptions of H_b



9, X = Cl, -N

were assigned to δ 2.45–2.5 for X = aziridinyl and to δ ~3.5 for X = Cl. These assignments are consistant with those reported for N-(β-chloroethyl)aziridine.[12]

The nmr spectra of the 1-N-aziridinylcycloalkenes exhibited a triplet δ 5.0, which is characteristic of the ethylenic proton on the enamine structure. This is one of the lowest downfield absorptions we have observed for an enamine ethylenic proton; it probably reflects a minimal interaction of the electron pair on the aziridinyl nitrogen with the olefinic π electrons. It is also interesting to note that the absorption of the protons on the aziridine ring appears as a singlet, which coincides with the cycloalkane protons. The nitrogen inversion is occurring too rapidly at room temperature to observe *syn* and *anti* conformers. The broad multiplet δ ~2.10 is due to the allylic protons on the cycloalkene ring.

Reactivity of the Aziridine Derivatives.—All of the compounds decomposed when stored at room temperature. The initial distillates darkened rapidly, and low-molecular-weight polyaziridine derivatives began to precipitate. The polymerization is probably initiated by the quaternary ammonium salt formed by the addition of N-(β-chloroethyl)cycloalkylimine to the bisaziridine component. Most of the polymers were insoluble in polar as well as acidic solvents which indicates that a cross-linked network had formed. Efforts to remove the N-(β-chloroethyl)cycloalkylimines by distillation and chromatography failed. However, when piperazine was added to the reaction mixture to convert the β-chloro derivative to a piperazinium salt, pure bis(aziridinyl)cycloalkane could be isolated. The purification of 1-N-aziridinyl-1-cycloheptene was effected by the same technique.

The nucleophilic character of the aziridinyl enamines was ascertained by allowing them to react with phenyl isocyanate in acetone. 1-N-Aziridinyl-1-cycloheptene (**10**) yielded a mixture of 2-aziridinyl-1-cycloheptene-1-carboxanilide (**11**), 2-aziridinyl-1-cycloheptene-1,3-dicarboxanilide (**12**), cycloheptan-2-one-1-carboxanilide (**13**), and cycloheptan-2-one-1,3-dicarboxanilide

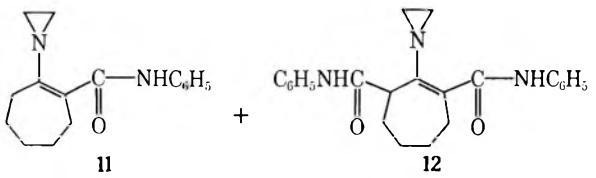
(10) H. T. Hoffman, Jr., G. E. Evans, and C. Glockler, *J. Amer. Chem. Soc.*, **73**, 3028 (1951). R. W. Hitchell, J. C. Burr, Jr., and J. A. Merritt, *Spectrochim. Acta*, **23A**, 195 (1967). J. Tempe, *C. R. Acad. Sci., Paris*, **259**, 1717 (1964); *Chem. Abstr.*, **62**, 1204 (1965).

(11) S. J. Brois, *J. Amer. Chem. Soc.*, **89**, 4242 (1967).

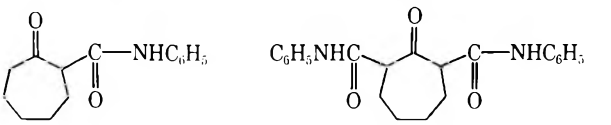
(12) P. L. Levins and Z. B. Papanastassiov, *ibid.*, **87**, 826 (1965).

(14). The reaction mixture was hydrolyzed with ethanolic hydrochloric acid to yield **13** and **14**, which were identical with the compounds obtained from the addition of phenyl isocyanate to 1-N-pyrrolidino-1-cycloheptene followed by acid hydrolysis. Treatment of 1-N-aziridinyl-1-cyclooctene with phenyl isocyanate afforded a mixture of mono- and diadducts as well as three minor components which were not identified.

10

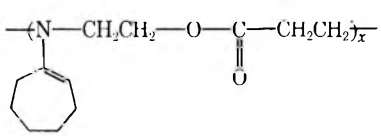


11 12



13 14

The reactivity of the aziridine substituent on the enamines is demonstrated by their polymerization when treated with β-propiolactone. An equimolar mixture of 1-N-aziridinyl-1-cycloheptene and β-propiolactone in acetonitrile yielded a low-molecular-weight yellow oil which was assigned structure **15** on



15

the basis of nmr and infrared evidence. The oil darkened rapidly when exposed to air as would be expected for a copolymer containing residual unsaturation. Recently, the reaction of N-phenylethylenimine and β-propiolactone under these conditions was reported to yield copolymers with a similar structure.[13]

Attempted Preparation of 1-N-Aziridinyl-1-cyclohexene.—The isolation and characterization of 1-N-aziridinyl-1-cycloheptene and -1-cyclooctene demonstrates the stability and bifunctionality of unsubstituted enamines containing an aziridine substituent. Since the titanium tetrachloride catalyzed addition of aziridine to cyclohexanone failed to afford 1-N-aziridinyl-1-cyclohexene (**16**), we attempted to prepare **16** *via* a base-catalyzed isomerization of 3-N-aziridinyl-1-cyclohexene. Isomerization of allylamines to enamines has been successfully employed in the synthesis of several N,N-dialkylenamines[14] and represents a technique for preparing *cis* isomers of monosubstituted aliphatic enamines.[15] The isomerization is catalyzed by potassium *t*-butoxide in dimethyl sulfoxide, sodium amide in liquid ammonia, or sodium metal. Since the aziridine ring is known to be resistant to strong bases, we did not anticipate any problems in isomerizing aziridine derivatives. We prepared 3-aziridinyl-1-cyclohexene (**17**) by allowing aziridine to react with 3-bromo-1-cyclohexene in the presence of powdered potassium hydroxide. Initially, we attempted to run the reaction at 0° in methanol, but no reaction occurred. Nonprotic solvents, such as nitrobenzene or chlorobenzene, produced low yields of the desired product, but the best solvent for the reaction proved to be tetralin. Although complete removal of the tetralin is extremely difficult, 60% yields of 3-aziridinyl-1-cycloheptene containing 15–20% tetralin could easily be obtained. Unfortunately, all attempts to isomerize this mixture to 1-N-aziridinyl-1-cyclohexene failed. The compound was essentially inert to potassium *t*-butoxide in dimethyl sulfoxide, sodium amide in liquid ammonia, and sodium metal at room temperature. Sodium amyloxide in benzene catalyzed a rapid decomposition. Prolonged heating of **17** in bulk or in *o*-chlorotoluene in the presence of sodium metal produces a low-molecular-weight polymer with residual unsaturation. However, no evidence for the characteristic ethylenic proton of an enamine structure could be detected in the nmr.

Experimental Section

Melting and boiling points are uncorrected. Analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. Ir spectra were determined using a Beckman IR-8 spectrometer. The nmr spectra were determined at 60 and 100 Mc with Varian Model A-60A and Varian HR-100 nmr spectrometers, respectively. The chemical shift values are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a Varian M-66 mass spectrometer operating at 70 eV. All reactions involving aziridine were performed under a nitrogen atmosphere. Thin layer chromatograms were obtained on 0.25-mm silica gel G plates developed by exposure to iodine vapor.

Preparation of Starting Materials.—Commercial samples of the starting carbonyl compounds were available. The aziridine was donated by the Dow Chemical Co. Benzene was distilled from calcium hydride. Reagent grade titanium tetrachloride was diluted with benzene to produce a solution which was 1 *M* in titanium tetrachloride. Phenyl isocyanate and β-propiolactone were purified by distillation immediately prior to use. 3-Bromo-1-cyclohexene was prepared by treating cyclohexene with N-bromosuccinimide in CCl_4.[16]

Illustrative Procedure for the Preparation of Bis(aziridinyl)-cycloalkanes.—A solution of 12 g (0.12 mol) of cyclohexanone in 100 ml of benzene was charged into a 1 l., four-necked, round-bottom flask equipped with a mechanical stirrer, nitrogen inlet, thermometer, and a pressure-equalizing dropping funnel. The dropping funnel was connected to a mercury pressure release valve; the system was purged and then placed under a positive pressure of nitrogen. The flask was immersed in an ice bath at 5° and 50 ml (0.36 mol) of triethylamine followed by 20 ml (0.44 mol) of aziridine were added. 1-N-Aziridinylcyclohexanol precipitated immediately. The slurry was stirred vigorously at 5–10° while 120 ml of 1 *M* $TiCl_4$ in benzene was added dropwise. Addition of the $TiCl_4$ required 1.5–2 hr. The reaction was stirred an additional 2–3 hr at 5°, and then the temperature was allowed to rise to 25°. The reaction mixture was allowed to stand overnight at room temperature. The volatile products were isolated from the mixture by filtering off the triethylamine hydrochloride, which had precipitated, evaporating the solvent and excess aziridine at reduced pressure, and distilling the residue through a short Vigreux column. A total of 9.5 g of volatile material, bp 75–78° (6 mm), was obtained. The composition

(13) T. Kagiya, T. Kondo, S. Narisawa, and K. Fukui, *Bull. Chem. Soc. Jap.*, **41**, 172 (1968).

(14) G. T. Martirosyan, M. G. Indzhikyan, E. A. Grigoryan, and A. T. Babayan, *Arm. Khim. Zh.*, **20**, 275 (1967); C. C. Price and W. H. Snyder, *Tetrahedron Lett.*, 69 (1962).

(15) M. Riviere and A. Lattes, *Bull. Soc. Chim. Fr.* 2539 (1967); J. Sauer and H. Prank, *Tetrahedron Lett.*, 2863 (1966).

(16) L. Horner and E. H. Winkelmann, *Newer Methods Preparative Org. Chem.*, **3**, 151 (1964).

of this product mixture was analyzed by tlc and nmr before further purification. A brown tar (4.2 g) remained in the distillation flask; this residue appeared to be an aziridine polymer. The relative concentrations of the volatile products (Table I) were determined by comparing the integrated areas of the δ 3.5, 2.5, and 1.12 absorptions. The value for bis(aziridinyl)cycloalkane was corrected for the overlapping aziridinyl absorption of **5**. Tlc on silica G with acetone as the eluent did not indicate the presence of components other than those reported in Table I.

Pure bis(aziridinyl)cyclohexane was obtained by stirring the distillate with 5.0 g of piperazine dissolved in 20 ml of benzene at room temperature overnight to remove **4**, filtering the precipitated salt, and fractionally distilling the filtrate *in vacuo*. After two distillations through a Vigreux column, 2.1 g of **3**, bp 58–60° (1.4 mm), was isolated: ir (neat) 3080, 1255, 805 cm^{-1} (aziridinyl); nmr (benzene) δ 1.12 (4.5 H triplet, *syn*-aziridinyl **H**), 1.43 (9 H singlet, cyclohexyl **H**), 1.80 (4.5 H triplet, *anti*-aziridinyl **H**); mass spectrum, no molecular ion, abundant fragment peaks at *m/e* 125, 124 (principal peak), 123, 122, 110, 96, 95, 94, 81, 80, 79, 77, 69, 68, 67, 56, 55, 54, 53, 43, 42, 41, and 39. *Anal.* Calcd for $C_{10}H_{18}N_2$: C, 72.23; H, 10.92; N, 16.85. Found: C, 72.53; H, 11.14; N, 16.44.

A similar purification procedure afforded pure **2**: bp 63° (3.0 mm); nmr (benzene) δ 1.32 (3.5 H, multiplet, *syn*-aziridinyl **H**), 1.45 (8.5 H, broad singlet, cyclopentyl **H**), 1.60 (4.0 H, multiplet, *anti*-aziridinyl **H**); mass spectrum, no molecular ion, fragmentation peaks at *m/e* 124, 110, 96, 67, 55, 54, 53, 52, 51, 44, 43, and 41 (principal peak). *Anal.* Calcd for $C_9H_{16}N_2$: C, 71.06; H, 10.52; N, 18.42. Found: C, 70.92; H, 10.18; N, 18.14.

β-(N-Aziridinylethyl)cyclopentylimine (**1**).—A mixture of cyclopentanone (50 ml, 0.6 mol) and aziridine (52 g, 1.2 mol) was allowed to stand at 30° for 1 week.[4] The excess aziridine was distilled from the light orange reaction mixture and the residue fractionally distilled under reduced pressure to yield cyclopentanone and 0.75 g of **1**: bp 85° (4.5 mm); ir (neat) 3080, 1250, 815 cm^{-1} (aziridinyl), 1710 cm^{-1} (C=N); nmr (benzene) δ 0.95 (2 H, triplet, *syn*-aziridinyl **H**), 1.51 (6 H, multiplet, *anti*-aziridinyl **H** and cyclopentyl $-CH_2-$ in the 3 and 4 positions), 2.00 (4 H, multiplet, allylic cyclopentyl $-CH_2-$), 2.52 (2 H, triplet, J = 7.0 cps, CH_2 adjacent to aziridinyl substituent), 3.48 (2 H, triplet, J = 7.0 cps, CH_2 adjacent of imine linkage); mass spectrum, 152 (molecular ion), 151, 137, 124, 123, 110 (principal peak), 96, 78, 77, 66, 56, 52, 51, 50, 42, and 41.

1-N-Aziridinyl-1-cycloheptene (**10**).—A mixture of cycloheptanone (34 ml, 0.3 ml) and triethylamine (150 ml, 1.1 mol) dissolved in 120 ml of benzene was allowed to react with 60 ml (1.5 mol) of aziridine for 30 min at 10°. A solution of 0.3 mol of titanium tetrachloride in 300 ml of benzene was added dropwise over a 3-hr interval while the temperature was maintained below 10° with an ice bath. When the $TiCl_4$ addition was completed, the reaction mixture was allowed to warm to room temperature (~35°) and stirred overnight. The product mixture, 18.5 g, bp 75–90° (3.3 mm), was isolated and analyzed by nmr as described above. Fractional distillation of the product mixture through a short Vigreux column yielded 7.8 g of a fraction, bp 56–59° (3.3 mm), which contained at least 70% **10** along with cycloheptanone and N-(β-chloroethyl)cycloheptylimine. This fraction was dissolved in 20 ml of benzene and treated with 1.0 g of piperazine at room temperature for 4 hr. Vacuum distillation of the benzene solution yielded 3.5 g of pure **10**: bp 69–71° (4.5 mm); ir (neat) 3080, 1280 cm^{-1} (aziridinyl), 1670, 763 cm^{-1} (C=C), nmr (benzene) δ 1.50 (10 H broad singlet, aziridinyl CH_2 and CH_2 at the 4, 5, and 6 positions of cycloheptenyl ring), 2.10 (4 H multiplet, allylic CH_2), 5.00 (1 H, triplet, ethylenic proton); mass spectrum, 137 (molecular ion), 136, 109, 108, 95, 94, 83, 82, 81, 80, 79, 68, 67, 56, 55, 54, 53, 42, and 41 (principal peak). *Anal.* Calcd for $C_9H_{15}N$: C, 78.76; H, 10.94; N, 10.21. Found: C, 78.53; H, 10.92; N, 10.51.

Reaction of 1-N-Aziridinyl-1-cycloheptene with Phenyl Isocyanate.—The enamine (1.54 g, 6 mmol) in 2 ml of acetone was allowed to react with 0.83 g (7 mmol) of phenyl isocyanate under nitrogen at 30° for 12 hr. Evaporation of the acetone yielded 1.55 g of a solid, mp 130–135°. Thin layer chromatography of this solid on silica gel G using a mixture of benzene–cyclohexane–absolute ethanol (25:60:10) revealed the presence of at least five components (R_f value): diphenylurea (0.00), **14** (0.21), **13** (0.32), **12** (0.47), and **11** (0.72). The mass spectrum of this mixture contained the molecular ions for **14**, **13**, and **11** at *m/e* 350, 231, and 256, respectively. Although a molecular ion for **12** was not observed, an ion at *m/e* of 333 was present which would correspond to the loss of aziridine (375 − 42) from this compound. The ir spectrum of the mixture had bands at 3080 (aziridinyl) and 1680 and 1660 cm^{-1} (–CONH–). Hydrolysis of 1.0 g of the mixture with 25 ml of 10% ethanolic HCl simplified the mixture to three components (tlc). These were identified as diphenylurea, **13**, and **14** by comparison with samples of these compounds prepared from 1-N-pyrrolidino-1-cycloheptene under the same conditions. Compound **14** (mp 193°) precipitated from the hydrolysis mixture; a mixture melting point with **14** prepared *via* the 1-N-pyrrolidino-1-cycloheptene showed no depression.

Reaction of 1-N-Aziridinyl-1-cycloheptene with β-Propiolactone—A solution of 1.4 g (2 mmol) of β-propiolactone in 10 ml of anhydrous acetonitrile was added to a glass ampoule and cooled to −78°. The enamine (0.8 g, 3 mmol) was injected through a serum cap after the ampoule had been filled with nitrogen. The ampoule was allowed to warm to 4°, and within 1 hr a yellow oil began to separate from the acetonitrile solution. After 2.5 days at 4°, the acetonitrile solution was decanted from the oil which was dried to constant weight (0.58 g) *in vacuo:* ir (neat) 1740 (–OOC–), 1670 cm^{-1} (C=C); nmr ($CDCl_3$) δ 4.65 (1 H, broad singlet, ethylenic proton), 4.30 (2 H, multiplet, $COO-CH_2$), 2.80 (10 H, multiplet, allylic CH_2, CH_2NCH_2-, $CH_2C=O$), 1.60 (6 H, broad singlet, CH_2 in the 4, 5, and 6 positions of the cycloheptene substituent). The polymer darkened rapidly upon exposure to air and the ethylenic proton disappeared.

Preparation of 3-N-Aziridinyl-1-cyclohexene (**17**).—3-Bromocyclohexene (21 g, 0.13 mol) was added to a mixture of 50 g (0.9 mol) of potassium hydroxide slurried in 200 ml of tetralin. The reaction mixture was cooled to 5° in an ice bath and stirred while 21 ml (0.4 mol) of aziridine was added dropwise. The addition required 0.5 hr; the mixture was stirred for 6 hr and then filtered. The yellow filtrate was fractionally distilled through a short Vigreux column under reduced pressure: fraction I, 15.0 g, bp 49–57° (7.0 mm); fraction II, 15.5 g, bp 62–67° (7.0 mm); fraction III, 75 g, bp 70–73° (7.0 mm). Fraction I contained 85.5% **17** (by nmr analysis), fraction II contained 28% **17**, and fraction III is essentially pure tetralin. Distillation of fraction I through a 30-cm spinning-band column failed to increase the purity of **17**. However, pure **17** could be obtained in much lower yield [3.0 g., bp 51–53° (11 mm)] by changing the solvent to chlorobenzene and isolating the 3-N-aziridinyl-1-cyclohexene as described above: ir (neat) 3050, 1280 (aziridinyl), 1660 cm^{-1} (C=C); nmr (CCl_4) δ 1.05 (2 H, broad doublet, *syn*-aziridinyl **H**), 1.58 (6.5 H, multiplet, cyclohexenyl CH_2), 1.96 (2.5 H, broad singlet, *anti*-aziridinyl **H**) 5.61 (2 H, broad singlet, ethylenic **H**). *Anal.* Calcd for $C_8H_{13}N$: C, 78.05; H, 10.57; N, 11.38. Found: C, 78.20; H, 10.87; N, 11.11.

Attempted Isomerization of 17 to 1-N-Aziridinyl-1-cyclohexene.—A solution of 0.3 ml of **17** in 3 ml of *o*-chlorotoluene was treated with 0.2 g of sodium metal and heated to 150°. The solution darkened rapidly, but nmr analysis showed that no enamine had formed after 24 hr at 150°. When N-allylmorpholine was treated under the same conditions, 60% isomerized within 1 hr to N-propenylmorpholine.[14] Treatment of **17** with a 20% solution of potassium *t*-butoxide in dimethyl sulfoxide at room temperature for 4 days or at 60° for 12 hr failed to effect isomerization.

Registry No.—Aziridine, 151-56-4; **1**, 23924-14-3; **2**, 23924-15-4; **3**, 23924-16-5; **10**, 23924-17-6; **17**, 23924-18-7.

The Synthesis of Oconovine

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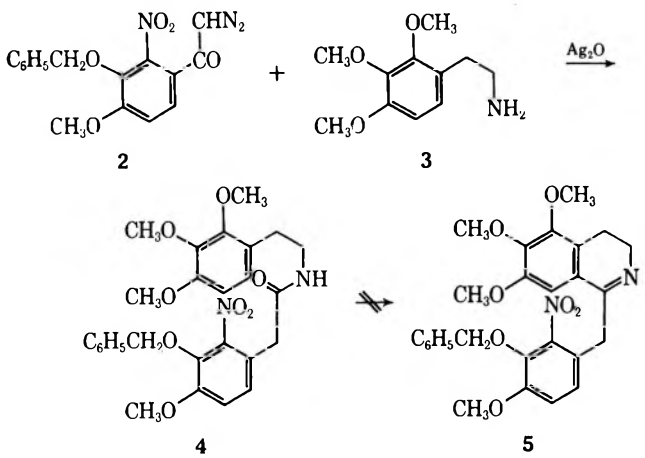
A synthesis is described for (±)-1,2,3,10-tetramethoxy-11-hydroxyaporphine (1). The latter proved to be the racemic form of the alkaloid (+)-oconovine, thus confirming the oconovine structure assigned earlier on the basis of spectroscopic evidence.

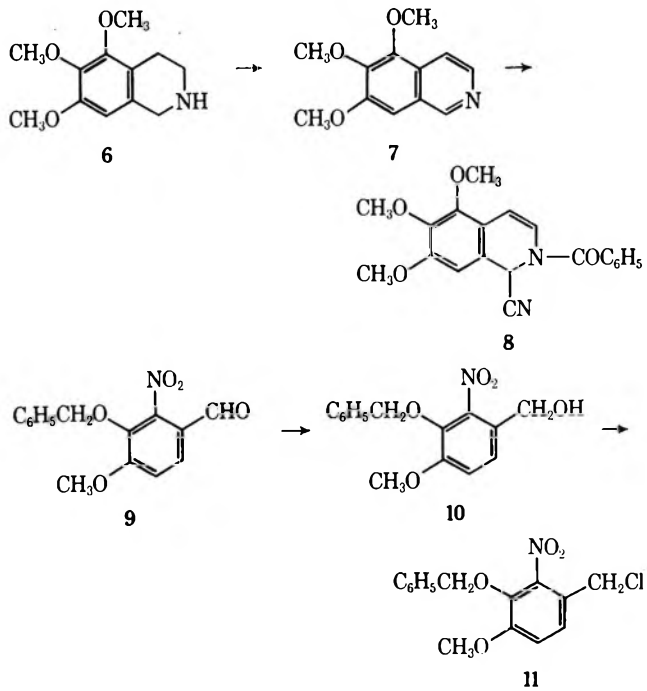
The amorphous base (+)-oconovine is one of two previously unreported alkaloids which have been found in an incompletely identified *Ocotea* species. Structure **1** was assigned to oconovine, primarily on the basis of spectroscopic evidence.[2] We now report the confirmation of this structure by a total synthesis of (±)-oconovine.

Since the proposed structure for oconovine (**1**) differs from that of isocorydine only by the presence of a 1-methoxy substituent, our first synthetic approach to oconovine was patterned after Kikkawa's successful isocorydine synthesis.[3] Thus decomposition of 2-nitro-3-benzyloxy-4-methoxy-ω-diazoacetophenone (**2**)[3] in the presence of 2,3,4-trimethoxy-β-phenylethylamine (**3**)[4] and silver oxide afforded an almost quantitative yield of the amorphous amide **4**, the nmr spectrum of which was fully in accord with the assigned structure. A number of attempts were made to cyclize this amide to the dihydroisoquinoline **5** under a variety of conditions; in all instances only nonbasic material was recovered.



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

In order to circumvent the use of the Bischler–Napieralski reaction, we turned to the alternate approach involving, as the key step, alkylation of the Reissert compound **8** by 2-nitro-3-benzyloxy-4-methoxybenzyl chloride (**11**). The latter halide was obtained by the sodium borohydride reduction of 2-nitroisovanillin benzyl ether[5] (**9**), followed by reaction of the resulting benzyl alcohol **10** with thionyl chloride. The Reissert compound **8** was prepared by the palladium dehydrogenation of 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline[6] (**6**) to 5,6,7-trimethoxyisoquinoline (**7**), followed by treatment of the latter base with benzoyl chloride and potassium cyanide. Alkylation



6 **7** **8** **9** **10** **11**

of **8** by halide **11** proceeded smoothly, using the general alkylation conditions of Kershaw and Uff,[7] to give the crystalline alkylated derivative **12**. Attempted hydrolysis of the alkylated Reissert compound **12** by alcoholic alkali in the usual manner[8] gave an unexpected yellow substance, mp 95–98°, which was assigned the substituted anthranil structure **14** on the basis of spectral data and elemental analysis. Hydrolysis of the Reissert derivative **12** to the desired isoquinoline **13** was achieved in excellent yield, however, by a new procedure using Triton B in dimethylformamide at room temperature. As expected, the isoquinoline **13** was converted into the anthranil **14** in high yield on refluxing with alcoholic alkali. The isoquinoline **13** was converted into its amorphous methiodide **15** by heating with methyl iodide in dimethylformamide in a sealed tube. Sodium borohydride reduction of methiodide **15** gave the tetrahydro derivative **16**, which was reduced by zinc in acetic acid to the amino tetrahydroisoquinoline **17**. Both of the latter compounds (**16** and

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(2) M. P. Cava, Y. Watanabe, K. Bessho, M. J. Mitchell, A. I. daRocha, B. Hwang, B. Douglas, and J. A. Weisbach, *Tetrahedron Lett.*, 2437 (1968).

(3) I. Kikkawa, *J. Pharm. Soc. Jap.*, **78**, 1006 (1958).

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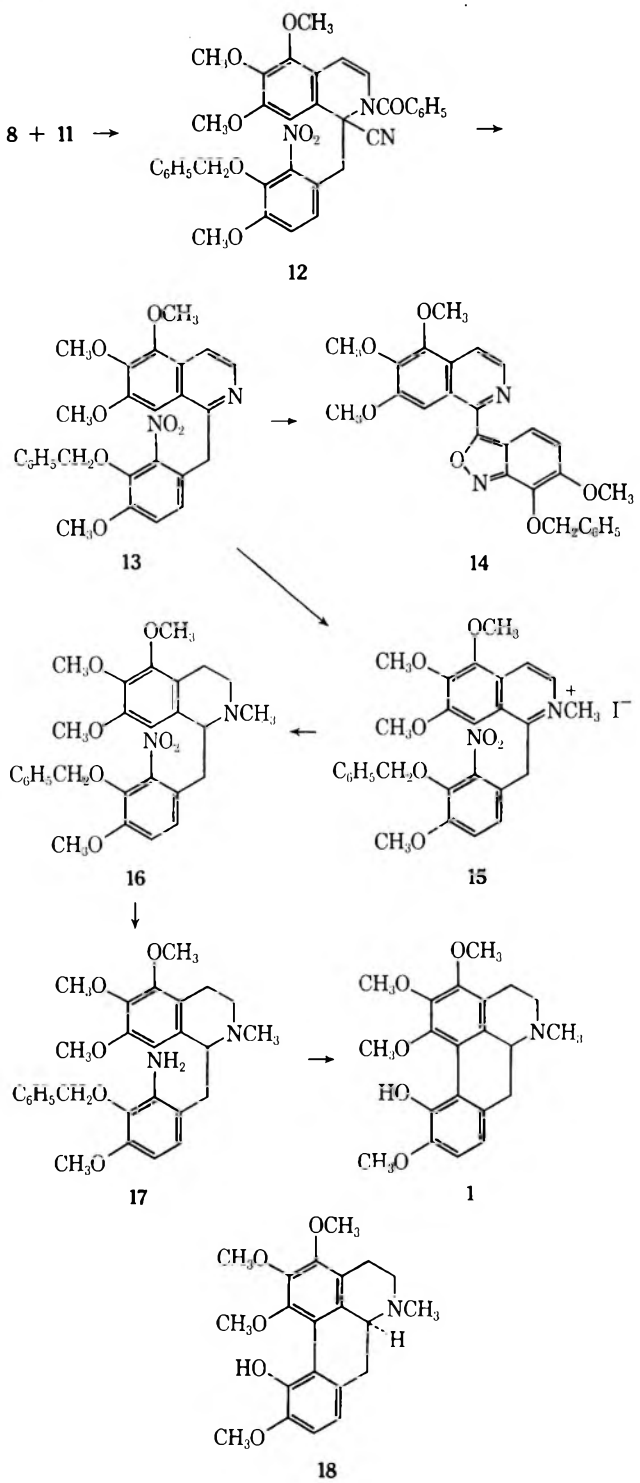
(6) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Eberman, *J. Org. Chem.*, **30**, 2248 (1965).

(7) B. C. Uff and J. R. Kershaw, *J. Chem. Soc., C*, 666 (1969).

(8) (a) F. D. Popp and W. E. McEwen, *J. Amer. Chem. Soc.*, **79**, 3776 (1957); (b) J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *Tetrahedron Lett.*, 3107 (1967). For a recent extensive review of the chemistry of Reissert compounds, see F. D. Popp *Advan. Heterocycl. Chem.*, **9**, 1 (1968).

17) were noncrystalline, but their nmr spectra were in accord with the assigned structures.

The Pschorr cyclization of amine **17** was effected by diazotization in dilute hydrochloric acid and slow decomposition of the resulting diazonium chloride at room temperature in the absence of a metal catalyst, followed by brief heating on the steam bath. Rather surprisingly, thin layer chromatography suggested that debenzylation had taken place during the Pschorr reaction with the direct formation of oconovine. Indeed, preparative chromatography led to the isolation of the amorphous base (±)-oconovine (**1**), which gave nmr, ultraviolet, and solution infrared spectra identical with those of the natural (+)-oconovine.



Like the natural base, racemic oconovine was further characterized as its crystalline methiodide.

No assignment of the absolute configuration of (+)-oconovine was made in the original publication describing its isolation.[2] It may be assumed to have the complete structure **18** on the apparently valid assumption that all dextrorotatory aporphines have the L (or *S*) configuration at the 6a carbon atom.[9]

Experimental Section[10]

2-Nitro-3-benzyloxy-4-methoxybenzyl Alcohol (10).—Sodium borohydride (0.15 g) was added in portions to a solution of 2-nitroisovanillin benzyl ether[5] (**9**, 2.0 g) in methanol (50 ml). When tlc indicated that the reduction was complete, the solvent was evaporated and the product was isolated in the usual manner to give alcohol **10** as a pale yellow gum which could not be crystallized: nmr δ 7.51 (s, 5 H, C_6H_5), 7.18 (AB q, 2 H, $\Delta\nu$ = 9 Hz, J = 9 Hz, aromatic), 5.20 (s, 2 H, $-OCH_2C_6H_5$), 4.58 (s, 2 H, $-CH_2OH$), 3.93 (s, 3 H, OCH_3), and 2.70 (s, 1 H, OH).

Alcohol **10** reacted with acetic anhydride in pyridine to give a crystalline O-acetyl derivative, mp 62° (ether–hexane).

Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.48; H, 5.30; N, 4.21.

2-Nitro-3-benzyloxy-4-methoxybenzyl Chloride (11).—Thionyl chloride (5 ml) was added to a solution of alcohol **10** (5.0 g) in benzene (50 ml) at room temperature. After 30 min, excess solvent and reagent were removed under reduced pressure and the residual oil was extracted with hexane. On cooling, the concentrated extract gave chloride **11** as a waxy solid (3.0 g, 56%), mp 41–45°. Analysis was not carried out because of the poor crystallization properties of the compound. The crude halide, however, was satisfactory for direct conversion into compound **12**.

5,6,7-Trimethoxyisoquinoline (7).—A solution of 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline[6] (**6**, 8.0 g) in purified (Al_2C_3) decalin (300 ml) containing suspended 10% palladium on charcoal (2 g) was refluxed for 7 hr under a CO_2 atmosphere. Extraction of the cooled mixture with aqueous hydrochloric acid and work-up of the basic product in the usual manner afforded isoquinoline **7** (7.85 g) as an oil which did not crystallize. The base was characterized as its crystalline picrate, mp 179°.

Anal. Calcd for $C_{18}H_{16}N_4O_{10}$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.11; H, 3.49; N, 12.37.

1-Cyano-2-benzoyl-5,6,7-trimethoxy-1,2-dihydroisoquinoline (8).—Benzoyl chloride (7 ml) was added dropwise to a vigorously stirred mixture of isoquinoline **7** (7.8 g), methylene chloride (70 ml), potassium cyanide (8.39 g), and water (10 ml); external ice cooling was maintaned during the addition. After an additional 4 hr of stirring, the organic phase was separated, washed with water, and evaporated. Trituration of the residual solid with ethanol afforded Reissert compound **8** (6.5 g, 60.5%), mp 162°. The analytical sample, mp 165°, was crystallized from ethanol.

Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.51; H, 5.22; N, 7.98.

1-(2-Nitro-3-benzyloxy-4-methoxy)benzyl-1-cyano-2-benzoyl-5,6,7-trimethoxy-1,2-dihydroisoquinoline (12).—Sodium hydride (1.07 g, 51% in mineral oil) was added to a solution of Reissert compound **8** (5.54 g) and chloride **11** (5.80 g) in dimethylformamide (130 ml) with external ice cooling. The mixture was stirred for 4 hr under nitrogen, diluted cautiously with water, and extracted with benzene. The usual work-up of the benzene layer, followed by crystallization of the residue from ethanol, afforded the alkylated Reissert compound **12** (6.86 g, 70%): mp 131°; nmr δ *ca.* 7.5–7.3 (m, 10 H, 2 C_6H_5), 7.08 (AB q, 2 H, $\Delta\nu$ = 9 Hz, J = 9 Hz, aromatic), 6.57 (s, 1 H, aromatic), 6.25 and 5.85 (vinylic doublets, 2 H, J = 8 Hz), 5.00 (s, 2 H, $-OCH_2C_6H_5$), 3.92 (s, 3 H, OCH_3), 3.90 (s, 6 H, 2 OCH_3), 3.72 (s, 3 H, OCH_3), and 3.6 (s, 2 H, CH_2Ar).

(9) M. Shamma and M. J. Hillman, *Experientia*, **25**, 544 (1969).

(10) Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points are uncorrected. Nmr spectra were run in $CDCl_3$ (TMS internal standard) using a Varian A-60 instrument; ultraviolet spectra were run in 95% EtOH unless otherwise stated, using a Perkin-Elmer Model 202 spectrophotometer.

Anal. Calcd for $C_{35}H_{31}N_3O_8$: C, 67.62; H, 5.03; N, 6.76. Found: C, 67.38; H, 5.28; N, 6.66.

1-(2-Nitro-3-benzyloxy-4-methoxy)benzyl-5,6,7-trimethoxyisoquinoline (13).—Triton B (7 ml, 40% methanolic benzyltrimethylammonium hydroxide) was added to a solution of compound **12** (5.78 g) in dimethylformamide (75 ml), and the mixture was kept at room temperature under nitrogen for 30 min. After dilution with ice and ether, concentrated hydrochloric acid was added until no further quantity of the hydrochloride of **13** separated. The salt was washed with ice–water and ether, and the free base **13** was liberated using ammonia. Crystallization from methanol gave **13** as white flakes (3.413 g, 75%): mp 120°; nmr δ 8.39 and 7.80 (d, 2 H, J = 6 Hz, aromatic), 7.4 (s, 5 H, C_6H_5), 7.10 (1 H), and 6.85 (2 H, both s, aromatic), 5.12 (s, 2 H, $-OCH_2C_6H_5$), 4.27 (s, 2 H, $-CH_2Ar$), and 4.02, 3.97, 3.93, and 3.83 (all s, OCH_3); uv λ_{max} 205 mμ (log ϵ 4.92), 245 (4.86), 283 (sh, 3.91), and 340 (3.72).

Anal. Calcd for $C_{27}H_{26}N_2O_7$: C, 66.11; H, 5.34; N, 5.71. Found: C, 66.39; H, 5.35; N, 5.63.

The hydrochloride of **13**, mp 183°, crystallized from ether–ethanol.

Anal. Calcd for $C_{27}H_{27}N_2O_7Cl$: C, 61.65; H, 5.17; N, 5.31. Found: C, 61.81; H, 5.28; N, 5.47.

Alkali Transformation Product (14) of Base 13.—Base **13** (0.120 g) was refluxed for 4 hr under a N_2 atmosphere with a solution of potassium hydroxide (0.5 g) in ethanol (20 ml). Evaporation of the solvent, addition of water, and crystallization from ethanol gave fluffy yellow crystals of the anthranil derivative **14** (0.088 g, 76%): mp 95–98°; nmr δ 8.63 and 8.25 (d, 2 H, J = 5 Hz, aromatic), 8.17 (s, 1 H, aromatic), 8.0–6.9 (miscellaneous aromatics), 5.55 (s, 2 H, $-OCH_2C_6H_5$), and 4.20 (6 H), 4.10 (3 H), and 3.95 (3 H), (all s, OCH_3); uv λ_{max} 2.12 mμ (log ϵ 4.83), 269 (4.30), and 305 (sh, 3.94).

Anal. Calcd for $C_{27}H_{24}N_2O_6$: C, 68.63; H, 5.12; N, 5.93. Found: C, 68.55; H, 5.16; N, 6.19.

Compound **14** was also formed directly from compound **12** under the experimental conditions given above.

1-(2-Nitro-3-benzyloxy-4-methoxy)benzyl-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (16).—A solution of isoquinoline **13** (0.050 g) in a mixture of dimethylformamide (0.5 ml) and methyl iodide (1 ml) was heated for 4 hr on the steam bath. Evaporation of the solvent mixture *in vacuo* left a gummy residue of methiodide **15**, which was washed with ether. A sample of **15** (0.100 g) was dissolved in ethanol (10 ml), and sodium borohydride (0.030 g) was added at room temperature. After 3 hr, work-up in the usual manner gave base **16** as a gum (0.050 g, 55%) which moved as a single spot on a silica plate [$CHCl_3$–EtOH (5:1)]: nmr δ *ca.* 7.4 (s, 5 H, C_6H_5), 6.90 (s, 2 H, aromatic), 6.13 (s, 1 H, aromatic), 5.13 (s, 2 H, $-OCH_2C_6H_5$), 3.87, 3.83 (6 H), and 3.71 (all s, OCH_3), and 2.40 (s, 3 H, NCH_3).

1-(2-Amino-3-benzyloxy-4-methoxy)benzyl-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (17).—A solution of nitro compound **16** (0.127 g) in a mixture of acetic acid (20 ml) and ethanol (10 ml) was stirred at room temperature for several hours with excess zinc dust. The basic reaction product was isolated in the usual manner. The portion of this material (0.075 g, 63%) which was extractable into hot hexane showed an nmr spectrum in accord with structure **17**: δ *ca.* 7.4 (m, 5 H, C_6H_5), 6.50 (s, 1 H, aromatic), 6.38 (AB q, 2 H, $\Delta\nu$ = 19 Hz, J = 9 Hz, aromatic), 4.95 (s, 2 H, $-OCH_2C_6H_5$), 3.90, 3.85 (6 H), and 3.70 (all s, OCH_3), and 2.40 (3 H, NCH_3).

(±)-Oconovine (1).—A solution of amine **17** (0.500 g) in a mixture of concentrated hydrochloric acid (1 ml) and water (15 ml) was cooled well in an ice bath, and a solution of sodium nitrite (0.100 g) in a small amount of water was added dropwise. After 30 min, sulfamic acid was added to destroy excess nitrous acid and the solution was allowed to warm up to room temperature. After standing overnight, the solution was heated for 15 min on the steam bath. Zinc dust was added to reduce colored by-products and the solution was heated for a further 15 min. The cooled and filtered solution was made basic with aqueous sodium hydroxide and extracted with methylene chloride to give 0.15 g of alkali-insoluble base mixture. The initial fractions (0.070 g) obtained by chromatography on neutral alumina ($CHCl_3$ eluent) showed no benzyloxy group by nmr analysis and were shown by tlc to be mostly oconovine. Reaction with methyl iodide, followed by crystallization from ethanol–ether, gave pure (±)-oconovine methiodide (0.050 g, 12.5%): mp 228°; uv λ_{max} 220 mμ (log ϵ 4.12), 278 (3.90), and 315 (sh, 3.49).

Anal. Calcd for $C_{22}H_{28}NO_5I$: C, 51.47; H, 5.50; N, 2.73. Found: C, 51.50; H, 5.56; N, 2.66.

In another experiment, amine **17** (0.492 g) afforded a product which was subjected to a final purification by silica chromatography in chloroform [$CHCl_3$–EtOH (20:1) as eluent] to give pure (±)-oconovine (**1**, 0.058 g, 15%): uv λ_{max} 280 mμ (log ϵ 4.03) and 310 (sh, 3.77); λ_{max} [ethanolic KOH (0.075 *N*) 280 mμ (log ϵ 3.87) and 335 (3.98).

The nmr spectrum of **1** was identical with that recorded for the natural base,[2] and the solution ($CHCl_3$) infrared spectra of the two samples were superimposable.

Registry No.—**1**, 23740-41-2; **1** methiodide, 23740-42-3; **7** monopicrate, 23740-79-6; **8**, 23740-80-9; **10**, 23740-81-0; **10** O-acetyl derivative, 23740-82-1; **11**, 23740-83-2; **12**, 23740-84-3; **13**, 23740-85-4; **13** hydrochloride, 23740-86-5; **14**, 23740-87-6; **16**, 23740-43-4; **17**, 23740-44-5.

Acknowledgment.—We are grateful to Dr. M. J. Mitchell for samples of compounds **2** and **3**. We also thank the Smith Kline and French Laboratories, Philadelphia, Pa., for generous financial support of this investigation.

Cleavage Reactions of Bicyclic Ketones Derived from Azoniaanthracene–Ketene Acetal Adducts

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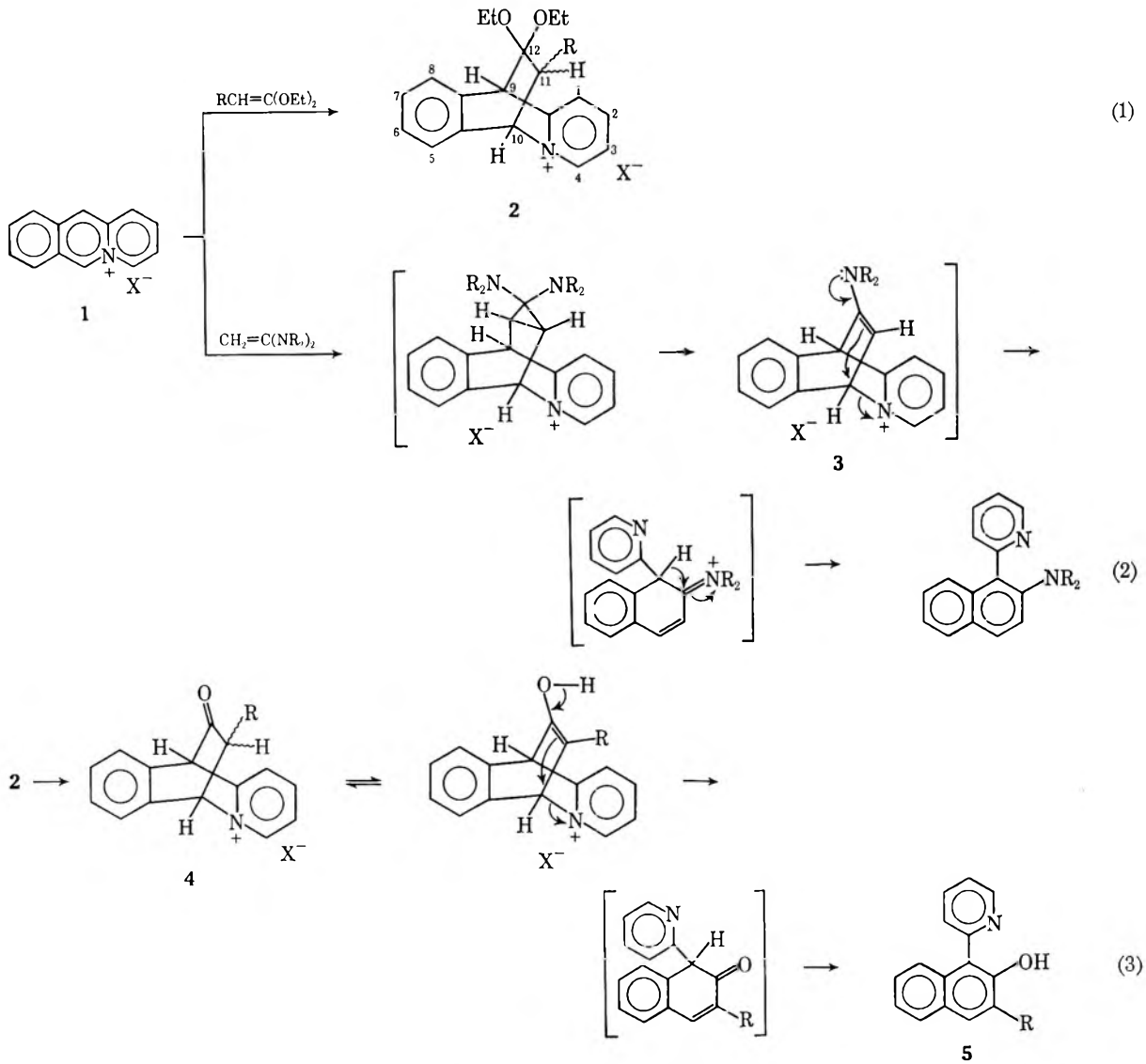
9,10-Dihydro-12-oxo-4a-azonia-9,10-ethanoanthracenes **4a–4c** were isolated following the mild acid hydrolysis of their respective ketals, **2a–2c**. Depending on the nature of the R group at C-11, **4** proved to be more or less labile to acidic as well as basic reagents, undergoing two distinctly different types of fragmentations to yield 1-(2-pyridyl)-2-naphthols (**5**) and/or 9,10-dihydro-10-(carboxymethyl)-4a-azoniaanthracene salts (**6**). Some structure–reactivity relationships were examined and a mechanism for these cleavages is suggested.

In a previous communication[1] ketene acetals were shown to react rapidly and stereoselectively by Diels–Alder addition with a variety of types of azoniapolycyclic aromatic compounds, *i.e.*, **1** → **2** (eq 1). Without exception, the cycloadditions gave the positional isomers with the alkoxy groups nonadjacent to the quaternary nitrogens as a mixture, where possible, of two geometrical forms in which the R group resides either *syn* or *anti* to the quaternary nitrogen. It was also shown that the reaction of 1,1-dimorpholinoethylene with the 4a-azoniaanthracene ion (**1**) readily gives 2-morpholino-1-(2-pyridyl)naphthalene (eq 2, R_2N = morpholino), probably resulting from an elimination reaction involving enamine **3** as an intermediate.



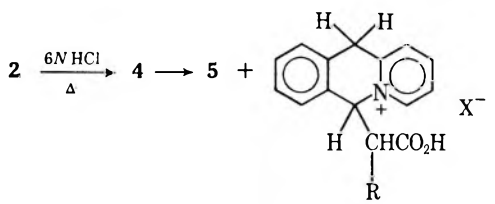
Noting the structural similarity of the enol of ketone **4**, a type of compound assumed to be available from **2** and enamine **3**, we thought it of interest to see if **4** would undergo an analogous elimination reaction, as indicated in eq 3, to give naphthol **5**. We now know that such a transformation is indeed quite feasible, and in fact it has been exploited in the syntheses of a number of highly overcrowded compounds to be described in several forthcoming publications. This

(1) D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.*, **35**, 390 (1968).

paper deals with an investigation of an unexpected and undesired second type of fragmentation of **4**-type ketones which was encountered during their preparation.

Results and Discussion

Acid Cleavages.—Treatment of the 4a-azoniaanthracene perchlorate–ketene diethyl acetal adduct, **2a**, with 6 *N* hydrochloric acid for 0.5 hr at reflux temperature afforded an easily separable mixture of two products (eq 4), neither of which was the expected bicyclo ketone, **4a**.



(4)

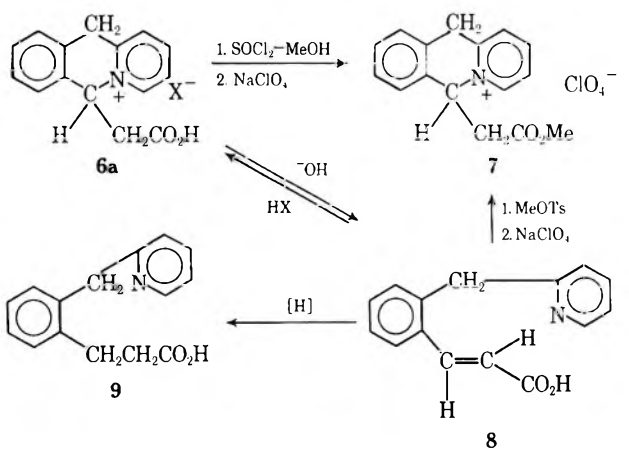
6

		Yield, %		
	R	4	5	6
a	H	0	9	84
b	Me	0	58	32
c	C_6H_5	15	80	0

The minor product, isolated in 9% yield, proved to be naphthol **5a**, based on elemental analyses of it and its O-acetyl derivative, and on the following spectral results. Its mass spectrum displayed a parent peak in agreement with the calculated molecular weight of 221. Its nmr spectrum ($CDCl_3$) consisted of a nine-proton multiplet at δ 7.17–8.35 (aromatic), a one-proton doublet of multiplets centered at δ 8.70 (pyridyl H α to N), and one exchangeable proton at δ 11.91 (–OH). The chemical shift of the hydroxyl proton is independent of concentration, indicative of intramolecular hydrogen bonding, consistent with the 1,2-substitution pattern assigned to **5a**. A comparison of the ultraviolet spectra of the acetyl derivative of **5a** and β-naphthyl acetate showed marked similarities.

The second product, obtained in 84% yield, was assigned structure **6a** based on elemental and spectral analyses of it and its derivatives shown in Scheme I.

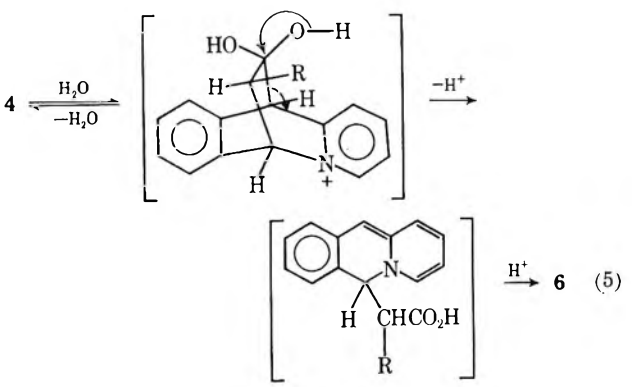
SCHEME I



Its nmr spectrum (DMSO-d_6) displayed the methylene protons α to the carboxyl group and adjacent to an asymmetric center (>$CHCH_2CO_2H$) as four peaks centered at δ 4.68, representing the center strong peaks of the AB portion of an ABX pattern. The remaining absorptions appeared as a two-proton singlet at δ 4.77 (α-picolinium methylene), a poorly resolved one-proton triplet centered at δ 6.50 (>$CHCH_2CO_2H$, X part of ABX), a seven-proton multiplet at δ 7.41–8.80 (aromatic), and a one-proton doublet of multiplets centered at δ 9.25 (pyridyl H α to N^+). Esterification of **6a** with methanol gave **7**. Treatment of **6a** with 0.5 *N* sodium hydroxide for 5 min at 100° followed by neutralization to pH 6.7 produced the *trans*-cinnamic acid (**8**), which in turn was catalytically reduced to **9**. Cinnamic acid (**8**), incidentally, was found to undergo cyclization to regenerate **6**-type products with particular ease. Its hydrochloride reverted without melting within 2 min at 175° to **6a** (X^- = Cl^-), and **7** was isolated following an attempted quaternization of **8** using 1 molar equiv of methyl *p*-toluenesulfonate in refluxing acetonitrile.

Similar fragmentations to **6**- and/or **5**-type products also resulted when the 11-methyl and 11-phenyl adducts, **2b** and **2c**, respectively, were treated with refluxing 6 *N* hydrochloric acid, although, as indicated by the yield data accompanying eq 4, the product distribution showed a considerable dependence on the nature of the R group at C-11.

A reasonable mechanism which will explain these results involves two competitive fragmentations of the intermediate bicyclic ketone **4**. As suggested earlier, **4** may cleave by an elimination sequence to give naphthol **5** (eq 3). Alternatively, **4** may suffer fragmentation by acid-catalyzed hydration of its carbonyl to give a 12,12-diol and cleavage of the 9,12 bond (eq 5). This

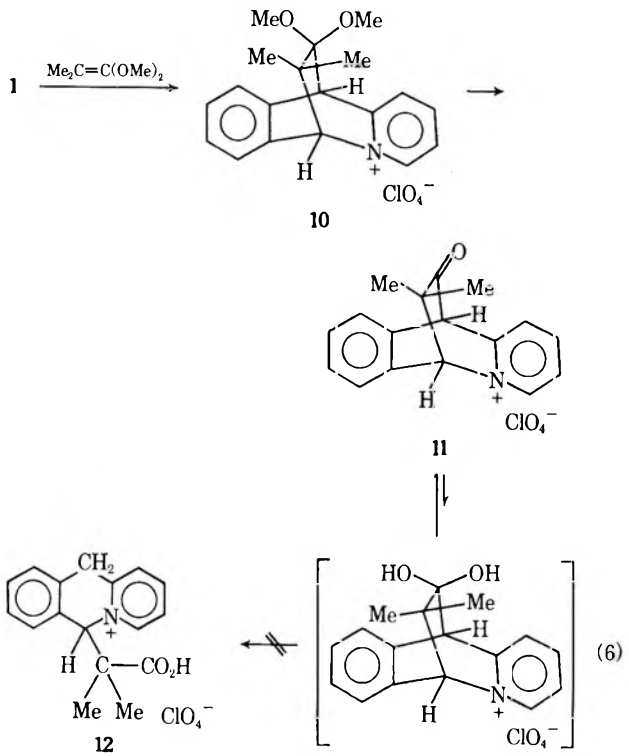


(5)

suggests that increasing the steric requirement of the R group at C-11 might well disfavor the production of **6**, since this would further enhance unfavorable steric interaction between the R group and the neighboring 12-hydroxyl groups, which are being held in an eclipsed conformation. This may at least partially account for the variation in yield of **6** from 84% when R = H (**6a**) to 32% when R = CH_3 (**6b**), and the concomitant increase in naphthol from 9 to 58% for **5a** and **5b**, respectively. On the other hand, if the enol of eq 3 plays an important role in the formation of the naphthol, then 11-phenyl substitution should favor naphthol formation owing to conjugative stabilization of the enol, as well as the aforementioned steric eclipsing effect. Experimentally, the fragmentation was considerably slower when R = C_6H_5 than when R = H or CH_3, and afforded, after 0.5-hr reflux in 6 *N* hydrochloric acid, naphthol **5c** and uncleaved **4c** in 80 and

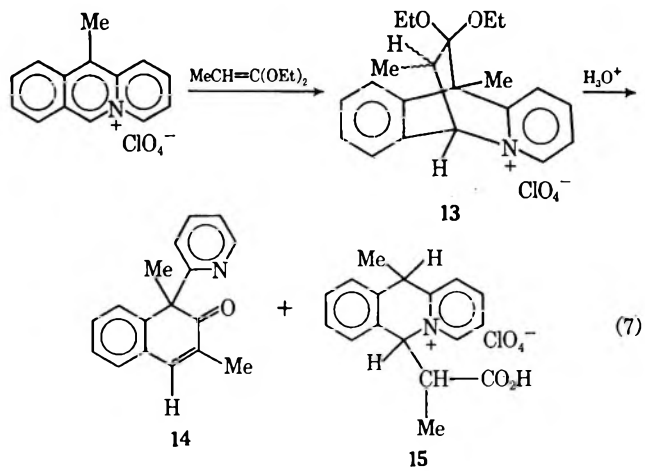
15% yields, respectively, while **6c**, if formed, was not detected.

Introduction of two alkyl substituents at C-11 will, of course, prevent naphthol formation, and an eq 5 type of cleavage would also be expected to be more difficult to effect based on steric considerations. This was substantiated in that bicyclo ketone **11** (eq 6), produced by heating for 0.5 hr at reflux a mixture of **10** and 6 *N* hydrochloric acid, proved to be completely stable to prolonged treatment (4 hr) under those same conditions. The steric strain inherent in the eclipsed geminal methyl–geminal hydroxyl intermediate leading to **12** should be reflected in a higher energy barrier for an **11** → **12** transformation than is encountered in the successful eq 5 type fragmentation of **4a** and **4b**, and it is evidently sufficient to prevent this type of cleavage under our reaction conditions. Ketal **10** has a similar eclipsed conformation, and indeed the Diels–Alder reaction that produced it was very sluggish compared with those involving less highly substituted ketene acetals.



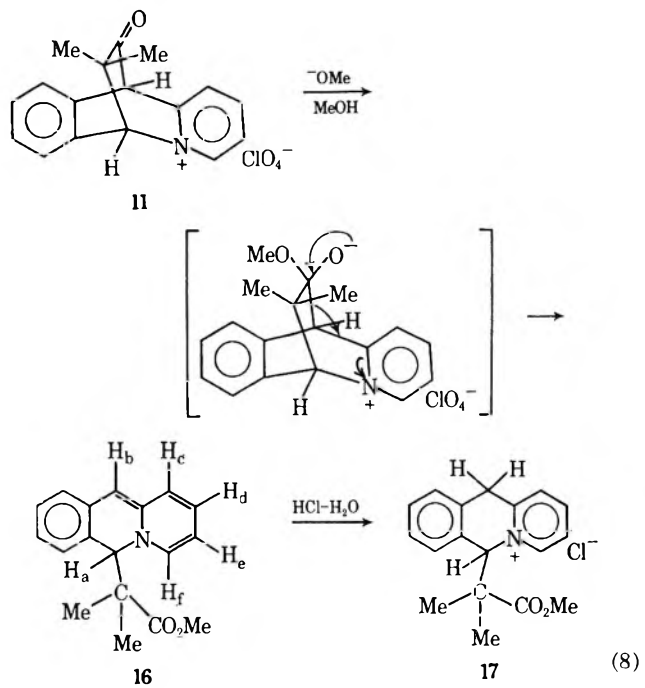
One other question briefly examined was whether or not the formation of an aromatic product, *i.e.*, naphthol **5**, provided the sole driving force for the elimination reaction. To this end adduct **13** was treated with 6 *N* hydrochloric acid for 1 hr at reflux temperature. A small amount (4%) of cyclic α,β-unsaturated ketone **14** was isolated in addition to **15** (89%) (eq 7).

Base Cleavages.—While our original hydrolysis experiments with **2a–2c** in refluxing 6 *N* hydrochloric acid resulted primarily in the fragmentation of initially formed **4a–4c**, these ketones were later obtained by employing milder hydrolysis conditions. We were thus able to examine their chemical behavior under basic conditions as well. The most obvious difference in behavior is that there is a much greater tendency to



fragment by cleavage of the 9,12 carbon–carbon bond than is operative under acidic conditions.

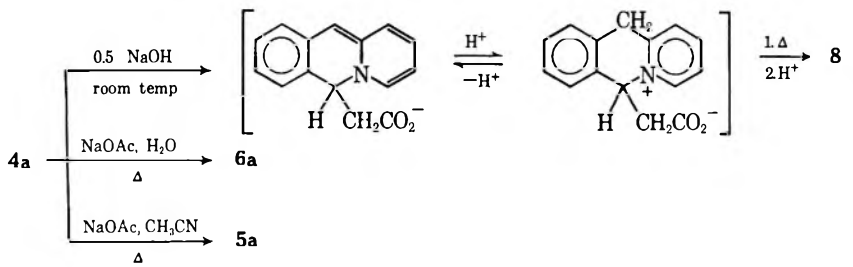
Our best demonstration of this was observed starting with bicyclic ketone **11**. Although **11** is stable to refluxing 6 *N* hydrochloric acid, it suffered immediate ring opening upon treatment with methanolic sodium methoxide at room temperature to give the red, crystalline anhydro base **16** (eq 8). Acidification of **16** with dilute hydrochloric acid produced pyridinium salt **17**.



Incidentally, the fact that **16** and **17** were derived from **11** provides chemical proof that the cycloaddition of 1,1-diethoxy-2-methylpropene with **1** occurred, giving the structure depicted for **10**. The method used in elucidating the structure of **2a–2c** and **13**, based on noting in their nmr spectra the multiplicities of the bridgehead hydrogens, was inapplicable to **10**, since there are no spin-coupling possibilities for either of its bridgehead hydrogens.

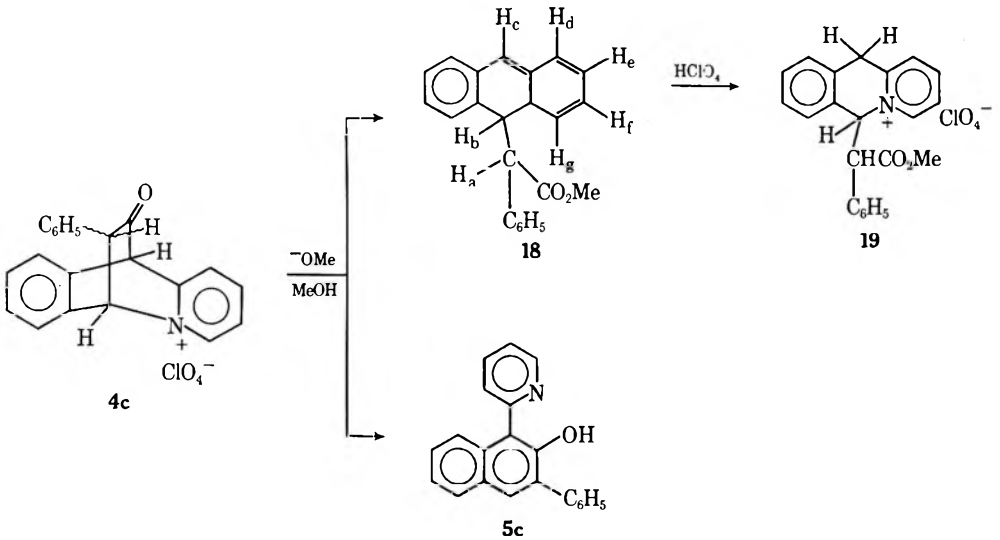
Cleavage of **4c** with methanolic sodium methoxide also occurred rapidly at room temperature to give anhydro base **18** and naphthol **5c** in 70 and 10% yields,

SCHEME II



respectively. This result also provides an interesting contrast to the incomplete fragmentation of **4c** by 6 *N* hydrochloric acid, which proceeded slowly even at 100° and gave only naphthol **5c**.

at room temperature by the very reactive potassium *t*-butoxide–water (10:3)–dimethyl sulfoxide reagent recently described by Gassman and coworkers.[2] However, this fragmentation was only two-thirds complete

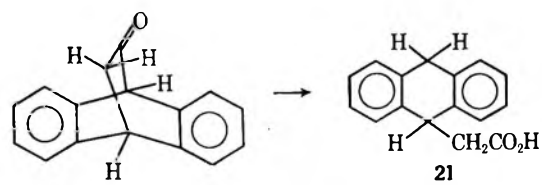


(9)

Weaker bases, including aqueous sodium hydroxide and even sodium acetate solutions, will produce these same types of results (see Scheme II). Treatment of **4a** with 0.5 *N* sodium hydroxide at room temperature immediately gave a blood-red solution characteristic of anhydro bases. This discolored to a pink solution upon warming, and afforded cinnamic acid **8** upon work-up of the reaction mixture. One molar sodium acetate solution, adequate for the cleavage reaction but not a strong enough base to effect a similar elimination, gave **6a** rather than **8** in 97% yield within 3 min at 100°.

Interestingly, since **6a** cannot be produced from **4a** under aprotic conditions, heating **4a** in a solvent such as acetonitrile or diglyme in the presence of anhydrous sodium acetate afforded naphthol **5a** in greater than 75% yield within 3 min at 80°, and the acetyl derivative of **5a** in quantitative yield within 3 min in refluxing acetic anhydride.

Undoubtedly, the extraordinary ease of cleavage of the 9,12 carbon–carbon bond of 9,10-dihydro-12-oxo-4a-azonia-9,10-ethanoanthracene salts such as **4a** by acidic and basic reagents is directly related to the ability of the pyridinium ring to stabilize a developing negative charge at C-9. A comparison of the ease of base cleavage of **20**, the hydrocarbon analog of **4a**, with cleavage results just cited for **4a** further emphasizes this fact. Ketone **20** was cleaved to **21** within 30 min after a 1-hr reflux period in the presence of sodium hydroxide in a diglyme–water mixture, and failed to



occur at all in the presence of either refluxing methanolic sodium methoxide or 6 *N* hydrochloric acid–diglyme solutions.

Experimental Section[3]

9,10-Dihydro-12-oxo-4a-azonia-9,10-ethanoanthracene Perchlorate (4a).—A heterogeneous mixture of **2a** ($X^- = ClO_4^-$

(2) P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Amer. Chem. Soc.*, **89**, 946 (1967).

(3) Melting points (uncorrected) were determined on a Thomas–Hoover apparatus. Ultraviolet absorption spectra were recorded on a Perkin-Elmer Model 202 spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrometer. Nmr spectra were determined with a Varian A-60 spectrometer on samples, unless otherwise stated, in dimethyl sulfoxide-d_6 solution with tetramethylsilane (TMS) as internal standard. Chemical shifts are recorded as parts per million to lower field from TMS (δ 0), followed by multiplicity, relative area, and assignment.

$^3/_4H_2O$)[1] (10.0 g, 0.0245 mol) in 40 ml of 6 *N* hydrochloric acid was allowed to shake for 3 hr at room temperature on a wrist-action shaker. A first crop of product (3.90 g) was collected by filtration and 3.50 g of additional crystalline product was obtained after diluting the filtrate with 40 ml of cold water and then treating it with solid sodium perchlorate. The combined product was washed with 5% sodium bicarbonate, dried, and then recrystallized from acetonitrile–ether as white needles, which proved to be an acetonitrile solvate of **4a**: mp 78–81°; ir 1740 cm^{-1} (C=O); nmr δ 2.10 (s, 3, CH_3CN), 3.00 (m, 2, C-11 methylene), 5.90 (s, 1, 9-bridgehead proton), 6.98 (broadened t, 1, 10-bridgehead proton), 7.45–9.03 (m, 7, aromatic H), and 9.45 (d, 1, pyridyl H α to N^+). This spectrum changed within 20 hr at room temperature to that of the ring-opened **6a**, after treatment of the sample in the nmr tube with a few drops of D_2O and 2 drops of 35% DCl.

Anal. Calcd for $C_{15}H_{12}ClNO_5 \cdot CH_3CN$: C, 56.3; H, 4.1; Cl, 9.8; N, 7.7. Found: C, 56.5; H, 4.0; Cl, 9.6; N, 7.5.

9,10-Dihydro-12-oxo-11-phenyl-4a-azonia-9,10-ethanoanthracene perchlorate (**4c**), mp 201–203°, was prepared in similar manner in 93% yield by treating 8.00 g of **2c**[1] with 75 ml of 6 *N* hydrochloric acid for 18 hr at room temperature on a wrist-action shaker. It was obtained as white needles after one recrystallization from nitromethane–ether: ir 1745 cm^{-1} (C=O); nmr δ 4.62 (s, 1, C-9 bridgehead), 6.10 (d, 1, C-10 bridgehead), 6.50–6.75 (m, 2, *ortho* hydrogens of 11-phenyl), 6.95 (d, 1, C-11 H), 7.18–8.77 (m, 1, aromatic H), and 9.34 (d, 1, H α to N^+).

Anal. Calcd for $C_{21}H_{16}ClNO_5$: C, 63.4; H, 4.0; Cl, 8.9; N, 3.5. Found: C, 63.0; H, 4.0; Cl, 9.3; N, 3.7.

Acid Cleavages of 2a–2c to 5- and 6-Type Products.—In a typical experiment a mixture of **2a** ($X^- = ClO_4^- \cdot {}^3/_4H_2O$) (5.00 g, 0.0123 mol) in 6 *N* hydrochloric acid was refluxed for 0.5 hr and the solution was then concentrated *in vacuo* to give a crystalline solid. The solid was dissolved in a mixture of 200 ml of 5% aqueous sodium bicarbonate solution and 100 ml of ether and the two layers were separated. The aqueous layer was acidified with concentrated hydrochloric acid and then treated with solid sodium perchlorate to yield 3.40 g (84%) of **6a**. An analytical sample melted at 201–203° after one recrystallization from water.

Anal. Calcd for $C_{15}H_{14}ClNO_6$: C, 53.0; H, 4.1; Cl, 10.4; N, 4.1; neut equiv, 340. Found: C, 53.1; H, 4.5; Cl, 10.3; N, 4.0; neut equiv, 336.

Concentration of the ether extract and recrystallization of the residue from methanol–water furnished 0.24 g (9%) of β-naphthol **5a** as white needles: mp 139–140°; uv max (CH_3CN) 228 mμ (log ϵ 4.88), 300 (sh, 3.83), 310 (383), and 349 (3.87); mass spectrum (70 eV) *m/e* 221 $(M)^+$, 220 $[(M - H)^+]$, and 192 $[(M - COH)^+]$.

Anal. Calcd for $C_{15}H_{11}NO$: C, 81.5; H, 5.0; N, 6.3. Found: C, 81.4; H, 4.8; N, 6.3.

Its O-acetyl derivative was obtained from ligroin (bp 60–90°): mp 113–114°; uv max (CH_3CN) 223 mμ (log ϵ 4.76), 270 (sh, 3.87), 279 (3.93), 287 (sh, 3.90), and 320 (3.10); ir 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.00 (s, 3, $-OCOCH_3$), 7.19–8.03 (m, 9, aromatic H), and 8.83 (doublet of multiplets, 1, pyridyl H α to N).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.8; H, 5.1; N, 5.3. Found: C, 78.1; H, 5.5; N, 5.2.

In similar manner acid cleavage of **2b** gave **6b** and **5b** in 32 and 58% yields, respectively, while **2c** afforded the naphthol **5c** in 80% yield, plus *ca.* a 15% yield of **4c**.

Pyridinium salt **6b** was recrystallized from acetonitrile–ether: mp 189–192°; nmr δ 1.08 (d, 3, methyl), 2.77–3.30 (m, 1, $>CH-CO_2H$), 4.77 (s, 2, α-picolinium methylene), 6.23 (d, 1, $>CH-CHRCO_2H$), and 7.40–9.41 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{16}ClNO_6$: C, 54.3; H, 4.5; Cl, 10.0; N, 4.0. Found: C, 54.3; H, 4.5; Cl, 10.3; N, 3.8.

Naphthol 5b, mp 62–64°, was obtained as yellow plates from petroleum ether: uv max (CH_3CN) 234 mμ (log ϵ 4.78), 310 (sh, 3.96), 318 (3.99), and 348 (3.91); nmr ($CDCl_3$) δ 2.40 (d, J = 1 Hz, 3, 3-methyl, long-range spin coupled to C-4 hydrogen), and 6.90–8.60 (m, 9, aromatic H).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.7; H, 5.5; N, 6.0. Found: C, 81.4; H, 5.1; N, 6.2.

Naphthol 5c was recrystallized as yellow plates from methylcyclohexane, mp 111–115°.

Anal. Calcd for $C_{21}H_{15}NO$: C, 84.9; H, 5.1; N, 4.7. Found: C, 84.5; H, 5.0; N, 4.9.

Methyl ester 7, mp 158–160°, was prepared by adding 1.0 g of **6a** to a cooled mixture of 2 ml of thionyl chloride and 15 ml of methanol. The resulting solution was allowed to stand at room temperature for 1 hr, heated at reflux for 1 hr, and concentrated to dryness. The residue was recrystallized as white needles from water: ir 1740 cm^{-1} (C=O); nmr δ 3.25 (4 peaks, 2, the center peaks of the AB part of ABX), 3.60 (s, 3, OCH_3), 4.77 (s, 2, α-picolinium CH_2), 6.53 (t, 1, X part of ABX), and 7.37–9.34 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{16}ClNO_6$: C, 54.3; H, 4.5; Cl, 10.0; N, 4.0. Found: C, 54.3; H, 4.9; Cl, 10.2; N, 3.9.

***trans*-Cinnamic Acid** (**8**).—The deep red solution initially formed upon dissolving **4a** (30.0 g, 0.11 mol) in 400 ml of 0.5 *N* sodium hydroxide solution discolored to a light pink during a 15-min reflux. Acidification of the solution to pH 6.7 with 0.5 *N* hydrochloric acid gave **8** as an oil, which crystallized upon scratching. The product was collected and recrystallized from acetone–water as white needles (14.8 g, 57%): mp 133–134.5°; nmr δ 4.27 (s, 2), 6.40 (d, 1, J = 16 Hz), 7.65 (d, 1, J = 16 Hz), 7.03–8.55 (m, 8), and one acidic proton, as shown by its rapid deuterium exchange.

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.4; N, 5.8; mol wt, 239. Found: C, 75.3; H, 5.8; N, 5.8; mol wt, 239.

Reduction of an ethanolic solution of **8** in a Parr hydrogenation apparatus in the presence of 5% palladium on charcoal gave **9**, mp 121–123° (monohydrate) after one recrystallization from water. Its ir and nmr spectra were consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{15}NO_2 \cdot H_2O$: C, 74.7; H, 6.2; N, 5.8. Found: C, 74.4; H, 6.5; N, 5.9.

9,12-Dihydro-12,12-dimethoxy-11,11-dimethyl-4a-azonia-9,10-ethanoanthracene Perchlorate (**10**).—A mixture of 4a-azoniaanthracene perchlorate[4] (**1a**, $X^- = ClO_4^-$, 5.34 g, 0.019 mol) and 1,1-dimethoxy-2-methylpropene[5] (20.0 g, 0.185 mol) in 50 ml of acetonitrile slowly reacted while shaking for 18 hr on a wrist-action shaker. The product (6.45 g, 85%) was precipitated by the addition of ether–ligroin (1:1, v/v) and recrystallized as white needles from water: mp 229–232°; nmr δ 0.90 (s, 6, C-11 methyls), 3.25 (s, 3, C-12 methoxyl), 3.30 (s, 3, C-12 methoxyl), 5.64 (s, 1, C-9 bridgehead proton), 6.17 (s, 1, C-10 bridgehead proton), and 7.37–9.41 (m, 8, aromatic H).

Anal. Calcd for $C_{19}H_{22}ClNO_6$: C, 57.7; H, 5.6; Cl, 9.0; N, 3.5. Found: C, 57.9; H, 5.3; Cl, 9.0; N, 3.5.

9,10-Dihydro-11,11-dimethyl-12-oxo-4a-azonia-9,10-ethanoanthracene perchlorate (**11**), mp 268–269° dec, was isolated as white needles in 87% yield after heating under reflux a mixture of **9** (3.50 g, 0.089 mol) in 50 ml of 6 *N* hydrochloric acid for 4 hr, followed by refrigeration of the mixture for 1 hr at 5°: ir 1740 cm^{-1} (C=O); nmr δ 0.90 (s, 3, C-11 methyl), 0.97 (s, 3, C-11 methyl), 5.97 (s, 1, C-9 bridgehead proton), 6.75 (s, 1, C-10 bridgehead proton), 7.50–8.97 (m, 7, aromatic H), and 9.47 (d, 1, pyridyl proton α to N^+).

Anal. Calcd for $C_{17}H_{16}ClNO_5$: C, 58.4; H, 4.6; Cl, 10.2; N, 4.1. Found: C, 58.2; H, 4.7; Cl, 10.1; N, 3.9.

9,10-Dihydro-9,11-dimethyl-12,12-diethoxy-4a-azonia-9,10-ethanoanthracene perchlorate (**13**), mp 165–171°, was prepared in 94% yield by the Diels–Alder addition of 1,1-diethoxypropene[5] with 9-methyl-4a-azoniaanthracene perchlorate[6] following a previously described procedure.[1]

Anal. Calcd for $C_{21}H_{26}ClNO_6$: C, 59.5; H, 6.1; Cl, 8.2; N, 3.3. Found: C, 59.9; H, 6.1; Cl, 8.4; N, 3.1.

Acid Cleavage of 13 to 14 and 15.—A solution of adduct **13** (4.00 g, 0.0095 mol) in 30 ml of 6 *N* hydrochloric acid was heated under reflux for 1 hr and then concentrated under reduced pressure to a crystalline solid. This residue was dissolved in a mixture of 200 ml of 5% aqueous sodium bicarbonate solution and 100 ml of ether. The aqueous layer was separated, acidified with concentrated hydrochloric acid, and treated with sodium perchlorate to give 3.08 g (89%) of crystalline **15**. Recrystallization from water gave white needles: mp 186–189°; ir 1710 cm^{-1} (C=O); nmr δ 1.08 (d, 3, C-9 CH_3), 1.92 [broadened d, 3, $-HC(CH_3)CO_2H$], 2.81–3.53 (m, 1, $>CHCO_2H$), 4.57–5.10 (m, 1, C-9), 6.30 (broadened d, 1, C-10), and 7.34–9.50 (m, 8, aromatic H).

(4) C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.*, **77**, 4812 (1955).

(5) S. M. McElvain and W. R. Davie, *ibid.*, **73**, 1400 (1951).

(6) C. K. Bradsher and T. W. G. Solomons, *ibid.*, **81**, 2550 (1959).

Anal. Calcd for $C_{17}H_{18}ClNO_6$: C, 55.5; H, 4.9; N, 3.8. Found: C, 54.9; H, 4.8; N, 3.6.

The ether extract was concentrated to a syrup, which subsequently crystallized. Recrystallization from methanol–water afforded 0.10 g (4%) of **14** as long, white needles: mp 99.5–100.5°; ir 1630 cm^{-1} (C=O); nmr δ 1.85 (s, 3 H), 2.01 (s, 3 H), 6.67–7.50 (m, 8, aromatic and olefinic protons), and 9.32 (doublet of multiplets, 1, pyridyl H α to N).

Anal. Calcd for $C_{17}H_{15}NO$: C, 82.0; H, 6.4; N, 5.6. Found: C, 81.7; H, 5.9; N, 5.7.

Base Cleavages of Bicyclic Ketones. A. Cleavage of 11.—The addition of sodium methoxide (0.40 g, 0.074 mol) to a suspension of **11** (0.70 g, 0.02 mol) in 10 ml of methanol gave immediately a red, crystalline precipitate. The mixture was diluted with 50 ml of water and filtered, and the product was recrystallized from acetone–water, giving 0.35 g (63%) of **16** as long, red needles: mp 104–106°; ir 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.12 and 1.22 (two s, 3 H each, *gem*-dimethyls), 3.65 (s, 3, ester methyl), 5.13 and 5.17 (two s, 1 H each, H_a and H_b), 5.30–5.61 (m, 1, H_e), 6.18–6.33 (m, 2, H_c and H_d), 6.50 (doublet of multiplets, 1, H_f), and 6.80–7.30 (m, 4, aromatic H).

Anal. Calcd for $C_{18}H_{19}NO_2 \cdot {}^1/_4H_2O$: C, 75.6; H, 6.7; N, 4.9. Found: C, 75.6; H, 6.8; N, 5.3.

The nmr spectrum of a sample of **16** in DMSO-d_6 and 3 drops of concentrated hydrochloric acid was completely consistent with structure **17**: δ 1.18 (s, 6, *gem*-dimethyl), 3.63 (s, 3, ester methyl), 4.70 (broadened s, 2, C-9 methylene), 6.55 (s, 1, C-10 H), 7.38–8.97 (m, 7, aromatic H), and 9.25 (d, 1, aromatic H α to N^+).

B. Cleavage of 4c.—Sodium methoxide (1.00 g, 0.0185 mol) added to a suspension of **4c** (2.00 g, 0.005 mol) in 10 ml of methanol immediately produced a red precipitate. The mixture was diluted with 15 ml of methanol–water (1:1, v/v) and filtered, and the residue (**18**) was air-dried and then recrystallized from ligroin (bp 60–90°) as red needles (1.02 g, 62%): mp 148–149°; uv max (CH_3CN) 238 mμ (log ϵ 4.37), 337 (sh, 3.28), 354 (3.60), 430 (4.16), 492 (3.76), and 522 (3.45); ir 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.41 (s, 3, ester methyl), 4.25 (d, 1, J = 10 Hz, H_a), 4.73–5.00 (m, 1, H_f), 5.20 (broadened d, 1, J = 10 Hz, H_b), 5.35 (s, 1, H_e), 5.69–6.25 (m, 3, H_d, H_e, H_g), and 6.87–7.57 (m, 4, aromatic H).

Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.2; H, 5.8; N, 4.3. Found: C, 79.9; H, 5.3; N, 4.3.

Acidification of a sample of **18** with dilute perchloric acid gave **19**, mp 202–206°, as white needles. Its nmr and elemental analyses were consistent with the assigned structure.

The aqueous filtrate from the initial cleavage reaction was acidified with 5% hydrochloric acid and then treated with 5% sodium bicarbonate to give an amorphous precipitate. Upon trituration in methanol this residue was converted into an off-white, crystalline product (0.15 g, 10%), which was identical in all respects with authentic 3-phenyl-1-(2-pyridyl)-2-naphthol (**5c**).

C. Cleavages of 4a (See Scheme II).—Heating under reflux a solution of **4a** ($X^- = ClO_4^-, \cdot CH_3CN$) (1.00 g, 0.0275 mol) in 50 ml of 0.5 *N* sodium hydroxide for 5 min transformed the initial deep red solution to a light pink one. Its neutralization to pH 6.7 gave **8** in 58% yield.

A mixture of 1.00 g of **4a**, 0.30 g of sodium acetate, and 10 ml of water was heated under reflux for 3 min, acidified with 5% hydrochloric acid, and treated with sodium perchlorate to give 0.88 g (97%) of **6a**.

Similarly, a mixture of 1.00 g of **4a**, 0.30 g of sodium acetate, and 10 ml of acetonitrile was heated under reflux for 3 min and then diluted with 50 ml of water to give **5a** in 75% yield.

D. Cleavage of 20.—A solution consisting of **20**[7] (2.00 g, 0.09 mol), potassium *t*-butoxide (3.00 g), 35 ml of dry methyl sulfoxide, and 0.35 ml of water was placed under nitrogen and allowed to stand at room temperature for 30 min. The red solution was acidified with 5% hydrochloric acid, producing a yellow, crystalline precipitate. This product was collected by filtration, dissolved in 5% sodium bicarbonate, and filtered, and the filtrate was again acidified with 5% hydrochloric acid, giving 1.91 g (88%) of off-white, crystalline **21**. An analytical sample, mp 159–168°, was obtained after one recrystallization from methylcyclohexane: nmr ($CDCl_3$) δ 2.61 (d, 2, J = 7 Hz, $-CH_2CO_2H$), 3.97 (d, 2, Ar_2CH_2), 4.50 (t, 1, J = 7 Hz, $>CHCH_2CO_2H$), and 11.57 (s, 1, $-CO_2H$).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.6; H, 5.9. Found: C, 80.8; H, 5.9.

Registry No.—**4a**, 23825-07-2; **4c**, 23825-08-3; **5a**, 23825-09-4; **5a** O-acetyl derivative, 23825-10-7; **5b**, 23825-11-8; **5c**, 23825-12-9; **6a**, 23825-13-0; **6b**, 23825-14-1; **7**, 23825-15-2; **8**, 23825-16-3; **9**, 23825-17-4; **10**, 23796-76-1; **11**, 23825-18-5; **14**, 23796-77-2; **15**, 23825-19-6; **16**, 23825-20-9; **17**, 23825-21-0; **18**, 23825-22-1; **19**, 23825-23-2; **21**, 23825-24-3.

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Reactions of Ketones and Related Compounds with Solid Supported Phosphoric Acid Catalyst. III. The Scope and Mechanisms of Phenyl Alkyl Ketone Reactions[1a]

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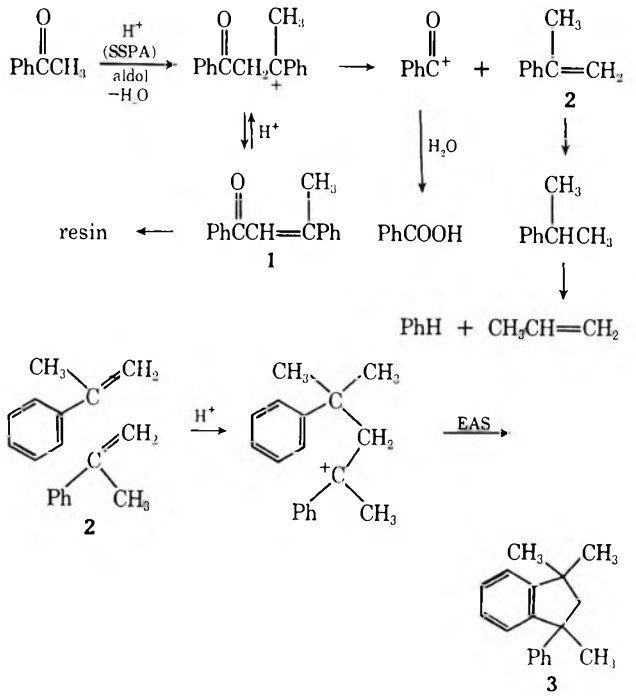
Rearrangement, condensation, disproportionation, and cyclodehydration reactions of phenyl alkyl ketones occur on solid supported phosphoric acid catalyst with good recovery of products. When the alkyl group is methyl or ethyl, disproportionation of aldol condensation products occurs to yield benzoic acid and fragments which eventually yield indans [1,1,3-trimethyl-3-phenylindan (**3**) or 1,1-dimethylindan, respectively]. When the alkyl group is larger than ethyl, functional-group rearrangement followed by cyclodehydration predominates. Butyrophenone and isobutyrophenone produce 1-methylindan in 18 and 43% yields, respectively, and *t*-butyl phenyl ketone gives 2,3-dimethylindene in 31% yield *via* its isomer, 3-methyl-3-phenyl-2-butanone. Significant rearrangement of both straight- and branched-chain alkyl phenyl ketones are observed; however, cyclization reactions seem to predominate in this system. 3-Phenyl-1-propanal cyclized to yield indene, which was reduced to indan (28% yield). Numerous alkenes and alkynes also give indenes and indans in good yields.

Earlier papers in this series[2,3] report the great utility of solid supported phosphoric acid (SSPA) in a flow reactor for catalyzing the rearrangement of aliphatic ketones to isomeric ketones. This research has now been extended to product, scope, and mechanistic studies for a group of phenyl alkyl ketones and related compounds. Rearrangements to isomeric ketones are observed, the primary compounds formed being cyclodehydration (indenes and indans) and disproportionation products from these rearranged ketones.

In previous studies,[4,5] acidic treatment of propiophenone and similar straight-chain aromatic aliphatic ketones gave only decomposition products and resins. Cyclizations of ketones with carbonyl groups α or β to the ring have not been observed previously. Branched-chain ketones such as isobutyrophenone[5,6] and pivalophenone[5,7] are known to rearrange to isomeric ketones, but their further cyclization has not been reported. Simons and Ramler[8] studied the reaction of several phenyl alkyl ketones with hydrogen fluoride and found that acetophenone and propiophenone formed benzoic acid and a resin, while isobutyrophenone produced only a resin.

The primary reaction of acetophenone on SSPA catalyst, after seven successive recycles at 360°, is the formation of 1,1,3-trimethyl-3-phenylindan (**3**, 20%) and benzoic acid (30%) (see Table I, run 1). Benzene and small amounts of cumene (9%) and α-methylstyrene (**2**, 4%) were also produced. These products could be formed by a disproportionation reaction, according to a reaction path similar to that proposed by Simons and Ramler[8] (Scheme I).[9] For reaction according to this sequence, dypnone (**1**) should give 1,1,3-trimethyl-3-phenylindan (**3**), α-methylstyrene (**2**),

SCHEME I



benzoic acid, cumene, and benzene; α-methylstyrene should give **3**, cumene, and benzene; and cumene should give benzene. When these compounds were subjected to the catalyst (Table I, runs 2–4), the expected products were formed; however, probably because of difficulty in forcing the high-melting material through the column rapidly, the major product from dypnone (**1**) was a resin. Perhaps acetophenone, formed from dypnone by a retrograde aldol condensation reaction, could have produced the hydrocarbons and benzoic acid by some other mechanism, but this is unlikely, especially in view of the excellent yield of **3** from α-methylstyrene (Table I, run 3).

The major products of the reactions of propiophenone and related compounds with SSPA catalyst are given in Table I. In an experiment (14 passes over the catalyst, 330°) in which there was a 60% recovery of liquid material, the following compounds were detected: propiophenone, 12%; methyl benzyl ketone, 8%; indan, 3%; 1,1-dimethylindan, 27%; a mixture of 1,2- and 1,3-dimethylindan, 5%; benzoic acid, 2%; ben-

(1) (a) Supported by U. S. Atomic Energy Commission Contract AT-(40-1)-3234; taken from the Ph.D. dissertation of F. E. J. (b) NASA Fellow, 1964–1966. (c) To whom correspondence should be addressed.

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(9) In this and the following formulations the ions are shown as open carbonium ions without specific discussion at this time of the accompanying solvation, counterions, etc.

TABLE I

YIELDS OF THE IMPORTANT PRODUCTS FROM THE MAJOR REACTIONS OF ACETOPHENONE, PROPIOPHENONE, AND RELATED COMPOUNDS WITH SSPA CATALYST

Run no.	Reactant	Products	No. of passes	Temp, °C	Yield,[a] %
1	Acetophenone	1,1,3-Trimethyl-3-phenylindan (3)	7	360	20
		Benzoic acid			30
2	Dypnone (1)	1,1,3-Trimethyl-3-phenylindan (3)	5	335	<1
		Benzoic acid			10
3	α-Methylstyrene (2)	1,1,3-Trimethyl-3-phenylindan (3)	5	350	55
4	Cumene	Benzene	5	350	16
5	Propiophenone	1,1-Dimethylindan	14	330	24
		Benzoic acid			2
6	Methyl benzyl ketone	Indan	7	360	4
		Propiophenone			6
7	1-Phenyl-1-propyne	Propiophenone	2	360	19.5
		Methyl benzyl ketone			5.5
		Indan			3
8	1-Phenyl-1-propene	*n*-Propylbenzene	3	360	<1
9	Allylbenzene	1-Phenyl-1-propene	2	360	39
10	3-Phenylpropanal	Indan	2	360	25
		Indene			3
11	Indene	Indan	3	319	49

[a] Based on the net amount of ketone reacted and on the stoichiometries in Scheme I or II.

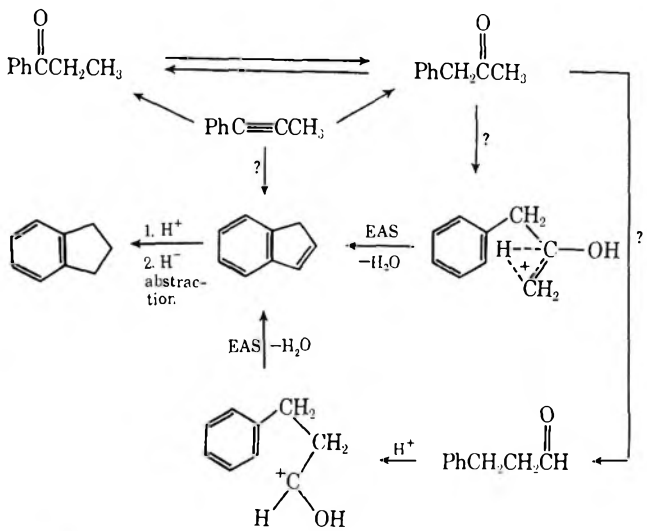
zene, 39%; ethylbenzene, 2%; 1-phenyl-1-propene, 1%; cumene, *n*-propylbenzene, and 1-methylnaphthalene, <1% each.

Neither the rearrangement of propiophenone to methyl benzyl ketone nor the conversion of either ketone into indan had been observed previously, but perhaps the most interesting reaction of propiophenone on SSPA catalyst is disproportionation to benzoic acid and 1,1-dimethylindan, 1,2-dimethylindan, 1,3-dimethylindan, and 1-methylnaphthalene. No path leading to these products involving the self-condensation of propiophenone and reasonable intermediates was evident. The reaction path shown in Scheme II involving an aldol condensation of propiophenone with its rearrangement isomer, methyl benzyl ketone (probably formed by an oxygen-function rearrangement[2,3]), yields the disproportionation products without going through usually high energy intermediates. This sequence is consistent with the observations that methyl benzyl ketone, 1-phenyl-1-propyne, allylbenzene, 3-phenylpropanal, and indene undergo the indicated rearrangement, hydration, reduction, and cyclization reactions (Table I, runs 6–11) and that the cross-aldol condensates of propiophenone with methyl benzyl ketone yield the disproportionation products on the catalyst (1–2.3% yield, not corrected for unreacted condensate) while the self-aldol condensates of each ketone do not.

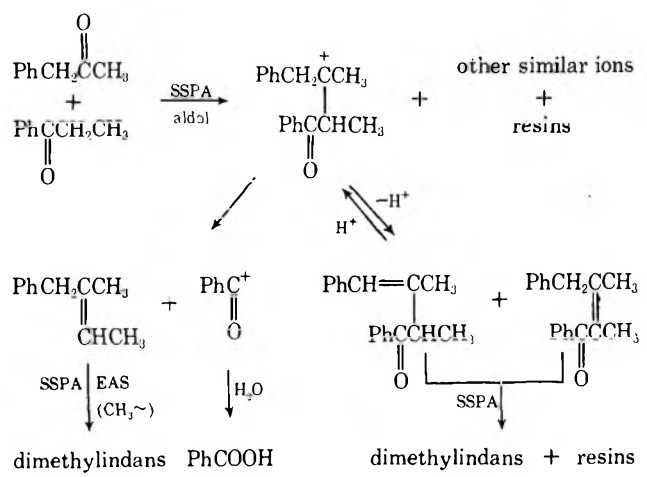
It is interesting to speculate about the mechanism by which an α or β functionally substituted aromatic compound such as propiophenone or methyl benzyl ketone may undergo cyclization at the γ position to a compound such as indene. The ketone rearrangements observed in this work provide a path from the α- to the β-substituted compounds. Further rearrangement to 3-phenylpropanal is unlikely, since aldehydes are known to rearrange to isomeric ketones with considerable facility.[4] Dehydration of methyl benzyl ketone to the nonconjugated 3-phenyl-1-propyne seems un-

SCHEME II

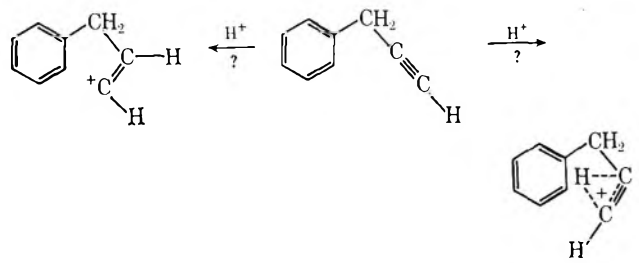
A. Rearrangement and Cyclization



B. Condensation, Disproportionation, and Cyclization

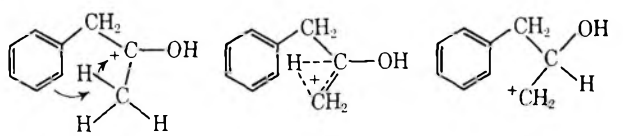


likely in the first place, but cyclization of the protonated, nonconjugated alkyne also seems unattractive, since the linear geometry of the alkyne would need to be altered drastically to permit ring closure. Energetic-



ally, the terminal vinyl cation is also an unattractive possibility.

A more likely cyclization path is the path through the protonated enol of methyl benzyl ketone, as is shown in Scheme II, part A. This protonated enol is seen to occupy an intermediate postion in the "proton-placement energy-barrier" sequence between the ketone conjugate acid and the primary carbonium ion formed by a hydride shift in the conjugate acid.



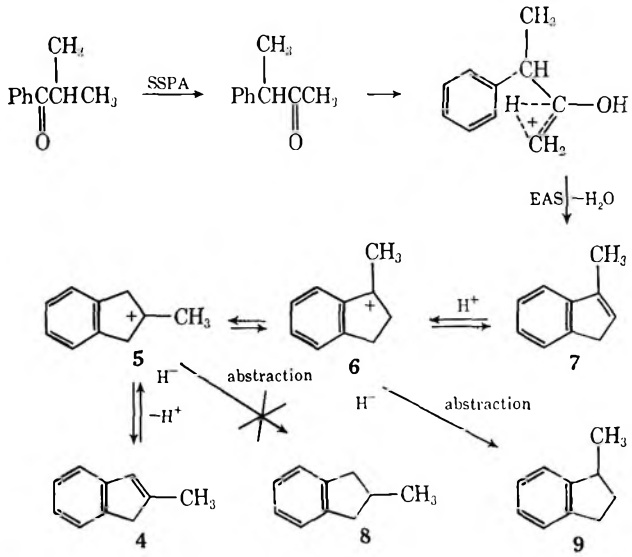
The ketone conjugate acid is undoubtedly formed first, and the terminal carbon atom clearly eventually takes on sufficient positive charge to interact with the ring electrons. Hydrogen, with an electron pair, must be transferred from the terminal carbon atom to the original carbonyl carbon. It is quite probable that the lowest energy path for this sequence of events will have the protonated enol at or near the energy maximum, and this species probably is the immediate precursor to the transition state for the cyclization reaction.

The primary reaction of isobutyrophenone with SSPA catalyst (Table II) (15 passes, 320°, 70% recovery of liquid material) was formation of 1-methylindan (**9**), which made up 59% of the recovered material (43% net yield). The remainder of the recovered material consisted of isobutyrophenone (13%), benzene (15%), 2-methylindene (**4**, 5%), 3-methylindene (**7**, 5%), naphthalene (1%), and 3-phenyl-2-butanone (1%). No cumene, isobutyric acid (from a deacylation), or benzoic acid (from a disproportionation reaction) was detected.

It is evident that cyclization *via* a carbon γ to the ring and a reduction step are required to give the major product, which, in this case, is obtained in preparatively useful yields. The simplest view of the reaction is show in Scheme III.

The first step in this sequence is clearly possible, since the rearrangement product, 3-phenyl-2-butanone, is one of the observed products. The amount of the rearranged ketone isolated was greater, 12%, when milder conditions were employed (300°, one pass), than the 1% obtained under more vigorous conditions (320°, 15 passes). The cyclization probably takes place through the protonated enol (see above), and the reduction through carbonium ion formation followed by hydride abstraction from the resinous decomposition

SCHEME III



material deposited on the catalyst [indene forms indan in good yield (Table I, run 11)].

It is interesting to note that no 2-methylindan (**8**) was detected despite a careful search. Thus, in contrast to 3-methylindene (**7**), 2-methylindene (**4**) (which is formed in 5% yield, the same as 3-methylindene) is not reduced to the corresponding indan **8**. It appears that the carbonium ion **5** formed by protonation of 2-methylindene (**4**) deprotonates or rearranges to the more stable conjugated ion **6** much faster than it undergoes the hydride abstraction reaction. The possibility that this reaction might proceed through the alkyne formed by dehydration of 3-phenyl-2-butanone is not particularly attractive, since the linear geometry of the alkyne would have to be altered drastically to permit ring closure (see above). In addition, despite a careful search neither 3-phenyl-1-butyne, nor its expected cyclization product, 1-methylindene, could be detected as reaction products.

The major reaction of butyrophenone (Table II, run 13) is cyclodehydration to the same products as obtained from isobutyrophenone, namely, 1-methylindan (**9**, 32% by glpc analysis of the total recovered liquid product), 3-methylindene (**7**, 8%), 2-methylindene (**4**, 5%), and naphthalene (9%). In addition, benzene (16%), 1-phenyl-2-butanone (5%), traces of butyric acid, and unidentified hydrocarbons (5%) were produced, with 20% of the butyrophenone unreacted. The most likely mechanism for the cyclodehydration would seem to involve oxygen function rearrangement[2,3] of butyrophenone to 1-phenyl-2-butanone and then to 4-phenyl-2-butanone followed by conjugate acid formation and cyclization to 3-methylindene (**7**) followed by reduction to 1-methylindan (**9**). The rearrangement to 1-phenyl-2-butanone was observed, and, when subjected to the catalyst (Table II, run 14), this ketone yields the same products as butyrophenone but in higher yields (7 passes, 21%, *vs.* 20 passes, 18% 1-methylindan). Similarly, when subjected to the catalyst (Table II, run 15), 4-phenyl-2-butanone formed the same products in even higher yields (3 passes, 31% 1-methylindan). In all of these reactions the amount of 3-methylindene relative to the amount of 1-methylindan decreases with each pass. This was

TABLE II

YIELDS OF THE IMPORTANT PRODUCTS FROM THE MAJOR REACTIONS OF ISOBUTYROPHENONE, BUTYROPHENONE, PIVALOPHENONE, AND RELATED COMPOUNDS WITH SSPA CATALYST

Run no.	Reactant	Products	No. of passes	Temp, °C	Yield, %
12	Isobutyrophenone	1-Methylindan	15	320	43
13	Butyrophenone	1-Methylindan	20	320	18
14	1-Phenyl-2-butanone	1-Methylindan	7	340	21
15	4-Phenyl-2-butanone	1-Methylindan	3	350	31
16	1-Phenyl-1-butyne	Butyrophenone	3	360	18
		1-Phenyl-2-butanone			3
17	4-Phenyl-1-butyne	1-Methylindan	2	360	32
18	4-Phenyl-1-butene	1-Methylindan	7	345	66
19	1-Phenyl-2-butene	1-Methylindan	2	360	79
20	Pivalophenone	2,3-Dimethylindene	5	360	35[a]
		1,2-Dimethylindan			17[a]
21	3-Methyl-3-phenyl-2-butanone	2,3-Dimethylindene	8	360	31[a]
		1,2-Dimethylindan			11

[a] Not corrected for recovered 3-methyl-3-phenyl-2-butanone.

especially noticeable with 4-phenyl-2-butanone, where the ratio of 3-methylindene to 1-methylindan went from 1.4 after the first pass to 0.23 after the third pass. These data support a mechanism involving ketone intermediates.

The yield (43%) of 1-methylindan from isobutyrophenone is higher than the yield (18%) from butyrophenone under comparable conditions (Table II, runs 12 and 13), even though the cyclization step would appear to involve a lower energy intermediate (the conjugate acid) in the butyrophenone case. Perhaps the ketone rearrangement steps are partially rate limiting, and the branched-chain compound reacts faster, or perhaps the methyl group of the ketone conjugate acid interferes sterically with the electrophilic attack on the ring.

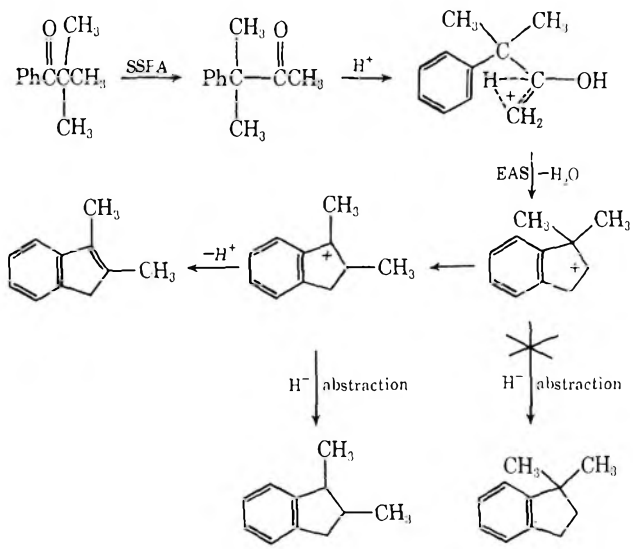
The possibility that the main cyclization mechanism for butyrophenone might involve alkyne intermediates was investigated (Table II, runs 16 and 17). After one pass over the SSPA catalyst, 1-phenyl-1-butyne was 75% converted into a mixture of butyrophenone and 1-phenyl-2-butanone, with only traces of 1-methylindan and 3-methylindene present. After three passes, most of the alkyne was gone, the main products were the two ketones, and the concentrations of 1-methylindan and 2-and 3-methylindene were beginning to build up. When 4-phenyl-1-butyne was subjected to the catalyst (Table II, run 17), the cyclization products were formed in good yield, and no ketones were detected. In both runs 16 and 17 the products could have been formed from the alkynes directly or from ketones produced by the hydration of the alkynes. It should be noted that the protonated form of 4-phenyl-1-butyne does not suffer from the geometrical cyclization difficulty mentioned above for other alkynes.

When 4-phenyl-1-butene and 1-phenyl-2-butene were subjected to the catalyst (Table II, runs 18 and 19), both formed 1-methylindan in excellent yield. However, no indenes were formed, ruling out unique paths involving alkene intermediates in the ketone and alkyne cyclizations.

When pivalophenone was subjected to the SSPA catalyst (Table II, run 20), extensive rearrangement to its isomer, 3-methyl-3-phenyl-2-butanone, occurred after one pass, but the expected cyclodehydration product from the isomeric ketone (1,1-dimethylindan) was not formed. Instead, a mixture (73% recovery of liquid material) containing 2,3-dimethylindene (46%) 1,2-dimethylindan (23%), 1-methylnaphthalene (3%) 1-methylindan (6%), and 13% of an unresolved mixture of 3-methyl-3-phenyl-2-butanone and 2-methylnaphthalene was obtained, 3-Methyl-3-phenyl-2-butanone was subjected to the SSPA catalyst (Table II, run 21) and gave the same products in approximately the same yields as pivalophenone.

It seems evident that pivalophenone first rearranges to 3-methyl-3-phenyl-2-butanone, which then cyclizes, as in Scheme IV. The isomerization of pivalophenone

SCHEME IV



to 3-methyl-3-phenyl-2-butanone is reported[10] to be 98% complete in 25 hr at room temperature with perchloric acid, demonstrating the ease with which this ketone rearranges.

Solid supported phosphoric acid catalyst has been shown to be an excellent medium for aliphatic ketone rearrangements.[2] However, results of the present research show that with phenyl alkyl ketones, rearrangement is followed by secondary reactions (disproportion-

(10) T. B. Remizova and T. E. Zalesskaya, *Zh. Obshch. Khim.*, **34**, 1395 (1964).

ation or cyclodehydration) which destroy the rearrangement isomer which is produced. When the alkyl moiety is larger than ethyl (*n*-propyl, isopropyl, *t*-butyl), rearrangement followed by cyclization to a methyl or dimethyl substituted indene predominates over condensation and disproportionation. The indenes which are thus produced are protonated and the carbonium ions formed abstract hydride ions (probably from polymeric material which builds up on the catalyst) to produce indans in good yield.

This catalyst seems to be an excellent medium for cyclizations. It has long been recognized[11,12] that most phenyl-substituted ketones and olefins polymerize (except for those giving a tertiary carbonium ion at the 3 position) before cyclizing in acid media. In addition, indenes, once formed, polymerize in most acid media.[13] However, on SSPA catalyst, cyclizations with good yields were observed even with compounds such as 1-phenyl-1-propyne, methyl benzyl ketone, 3-phenyl-1-propanal, and numerous phenyl-substituted butanones, butynes, and butenes which would polymerize in other acid media.

In many cases, treatment of the appropriately substituted olefins with SSPA catalyst appears to be the method of choice for the preparation of substituted indans.

Experimental Section

General Experimental Technique and Instrumentation.[14]—A complete description of catalyst preparation, reactor, and recovery systems and gas chromatographs used in this study has been given in a previous paper of this series.[2] The weight ratio of 85% phosphoric acid to support (Chromosorb W, Johns-Manville) ranged from 4.5:1 to 6:1 with little difference in catalyst activity noted. A flow rate of 65 ml/hr of reactant over a bed of *ca.* 90 g of catalyst was used, with a nitrogen carrier flow rate of 5–10 ml/min (mean residence time *ca.* 10–20 min).

The weight percentage values for the various products were calculated by glpc analysis using *n*-propylbenzene as an internal standard according to the technique of Lo Chang and Karr.[15] The chemical yields were then calculated from these weight percentage values, the total weight of the liquid sample being analyzed (corrected for nonvolatile residues which were not included in the glpc analyses), and the stoichiometries of Schemes I–IV. For separable solid compounds, *e.g.*, benzoic acid, the weights were measured directly.

Reactions of Acetophenone and Related Compounds.—Acetophenone (50 ml) was passed seven times over the catalyst at 360 ± 5°. The 30 ml of liquid product recovered was washed with ammonium hydroxide, and 6.0 g of benzoic acid was recovered from the basic extract. The organic layer was dried, filtered, and distilled. Six fractions were collected and 7.1 g of residue remained in the kettle. Fraction 1, bp 65–80° (735 mm), 5.0 g, was essentially pure benzene. Fraction 2, bp 80–120° (735 mm), 2.1 g, contained cumene and α-methylstyrene, which were separated by preparative glpc on a QF-1 column and identified by their spectra. Fractions 3 and 4 were mainly unreacted acetophenone. Fraction 5, bp 134–140° (10 mm), 1.2 g, was essentially pure 1,1,3-trimethyl-3-phenylindan (**3**): mp 51–52°; n^{25}D 1.5682 [lit.[16] mp 52–53°; bp 155° (12 mm); n^{20}D 1.56809]; ir (CCl_4) 1380 cm^{-1} (geminal dimethyl); nmr $\delta_{TMS}^{CCl_4}$ 1.01 (s, 3 H, CCH_3), 1.30 (s, 3 H, CCH_3), 1.63 (s, 3 H, CCH_3), 2.15 (d, 1 H, CH), 2.41 [d, 1 H, CH, $J_{AB/(B-A)}$ = 0.33 Hz (indicating[17] protons on the same carbon but in different environments, theoretical value 0.37], and 7.03 and 7.07 (two overlapping singlets, 9 H (C_6H_4 and C_6H_5). The ir and nmr spectra of compound **3** are identical with those of 1,1,3-trimethyl-3-phenylindan prepared by subjecting α-methylstyrene to the catalyst. Dypnone, α-methylstyrene, and cumene were subjected to the catalyst and the products were separated and identified in the same manner as described for acetophenone.

Reactions of Propiophenone and Related Compounds.—The commercial propiophenone used was first purified by preparative glpc. A 50-ml sample of the ketone was passed over the catalyst 14 times at 330° with a recovery of 30 ml of liquid. The product was worked up and distilled, and the components were separated by glpc on SE-30 and QF-1 preparative columns. Benzene, ethylbenzene, cumene, *n*-propylbenzene, indan, 1-phenyl-1-propene, and methyl benzyl ketone were isolated and identified by comparison of their ir and nmr spectra and glpc retention times on several different columns with those of authentic samples. A component of the fraction with a boiling point of 58–74° (10 mm), 7.91 g, was isolated on a QF-1 column at 150°, giving 2.2 ml of pure 1,1-dimethylindan: n^{20}D 1.5140 (lit.[18] n^{20}D 1.5141); ir (neat) 1376 and 1355 cm^{-1} (geminal dimethyl); nmr $\delta_{TMS}^{CCl_4}$ 1.20 [s, 6 H, $C(CH_3)_2$], 1.83 (t, 2 H, J = 7.5 Hz, CH_2), 2.82 (t, 2 H, J = 7.5 Hz, CH_2), and 6.98 (s, 4 H, C_6H_4); mass spectrum (70 eV) *m/e* (rel intensity) 146 (14.7), 131 (100), 116 (7.7), 115 (14.4), 91 (19.3), 77 (7.6), 51 (8.6), and 39 (8.9). A mixture of 1,2- and 1,3-dimethylindan was obtained by preparative glpc (SE-30 column). All of the major infrared peaks of both indans match those for the two pure indans.[19] The nmr spectrum indicates that both dimethylindans are present: $\delta_{TMS}^{CCl_4}$ 1.16 (d, 3 H, $CHCH_3$, 2-methyl of 1,2-dimethylindan) 1.25 (d, 3 H, $CHCH_3$, 1-methyl of 1,2-dimethylindan), 1.28 (d, 6 H, $CHCH_3$, 1- and 3-methyls of 1,3-dimethylindan), 1.5–3.2 (m, CH_3CH and CH_2), 6.97 (s, 4 H, C_6H_4), and 7.01 (s, 4 H, C_6H_4). A positive Jones oxidation of the mixture indicates the presence of benzylic hydrogens. Further separation of this mixture by preparative glpc gave nearly pure 1,2-dimethylindan (determined by ir and nmr spectra). 1-Methylnaphthalene, still somewhat impure, was obtained by preparative glpc.

Methyl benzyl ketone, 3-phenylpropanal, 1-phenyl-1-propene, allylbenzene, and indene were treated with the catalyst and their products were separated by glpc and analyzed in the same manner as described above.

Aldol condensates of propiophenone, of methyl benzyl ketone, and of a 2.7:1 molar mixture of propiophenone with methyl benzyl ketone were prepared[14] using gaseous HBr. The three condensates (30 g) were mixed with equal volumes of benzene, and 1 ml of water and passed over the catalyst six times. A sample (0.005 ml) of the reaction mixture was analyzed by glpc after each pass.[14] Benzoic acid was extracted after the last pass with 20% NH_4OH and precipitated with dilute HCl.

Identification of Isobutyrophenone, Butyrophenone, and Pivalophenone Reaction Products.—Isobutyrophenone, butyrophenone, pivalophenone, and related compounds were passed over the catalyst, and the reaction mixtures were worked up and analyzed in the usual way.

Benzene, naphthalene, and 3-phenyl-2-butanone were isolated in pure form from the recovered isobutyrophenone reaction mixture and identified by their ir and nmr spectra. A distillation fraction, bp 67–68° (10 mm), contained 1-methylindan, which was purified by glpc: n^{25}D 1.5145 [lit.[19] bp 60–70° (12 mm); n^{25}D 1.5241]; nmr $\delta_{TSM}^{CCl_4}$ 1.19 (d, 3 H, $CHCH_3$), 1.60 (m, 1 H, CHH), 2.12 (m, 1 H, CHH), 2.60–3.28 (m, 3 H, CH_2 + $CHCH_3$), and 6.98 (s, 4 H, C_6H_4); ir and uv spectra identical with those of 1-methylindan;[19] mass spectrum (70 eV) *m/e* (rel intensity) 132 (31), 131 (30.7), 130 (20.5), 117 (100), 91 (18.1), 77 (10.9), and 63 (13.6). 3-Methylindene was separated by glpc from a fraction with a boiling point of 68–88° (10 mm) [lit.[20] bp 70° (10 mm)]; nmr $\delta_{TMS}^{CCl_4}$ 2.12 [s (fine splitting), 3 H, C=CCH_3], 3.20 [s (fine splitting), 2 H, CH_2], 6.04 [s (fine splitting), 1 H, C=CH], and 6.95–7.2 (m, 4 H, C_6H_4); ir spectrum identical with that of 3-methylindene;[21] mass spectrum (70 eV) *m/e* (rel

(11) M. Bogert and D. Davidson, *J. Amer. Chem. Soc.*, **56**, 185 (1934).
(12) W. von Miller and G. Rhode, *Chem. Ber.*, **23**, 1881 (1890).
(13) C. Bradsher, *Chem. Rev.*, **38**, 447 (1946).
(14) See F. E. Juge, Jr., Ph.D. Dissertation, University of Arkansas, 1967, for full experimental details.
(15) Lo Chang and C. Karr, Jr., *Anal. Chim. Acta*, **21**, 474 (1959).
(16) E. Bergman, H. Taubadel, and H. Weiss, *Chem. Ber.*, **64**, 1493 (1932).
(17) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 3rd ed, The Macmillan Co., Inc., New York, N. Y., 1963, p 90.
(18) J. W. Wilt and C. A. Schneider, *J. Org. Chem.*, **26**, 4196 (1961).
(19) J. Entel, C. H. Ruof, and H. C. Howard, *Anal. Chem.*, **25**, 1303 (1953).
(20) E. Rodd, "Chemistry of Carbon Containing Compounds; A Modern Treatise," Vol. 12A, Elsevier Publishing Co., Amsterdam, 1962, p 107.
(21) American Petroleum Institute, "Catalog of Infrared Spectral Data," Serial No. 1598, Project No. 44, Carnegie Institute of Technology, Pittsburg, Pa.

intensity) 130 (100), 129 (64.9), 138 (36.6), 127 (17.6), 115 (97.5), 77 (15.4), 65 (12.7), 63 (21.8), 51 (29.3), and 39 (20.9). 2-Methylindene was isolated by glpc from the same fraction [lit.[20] bp 79° (10 mm)]: nmr $\delta_{TMS}^{CCl_4}$ 2.10 [s (fine splitting), 3 H, C=CCH$_3$], 3.17 (s, 2 H, CH$_2$), 6.36 [s (fine splitting), 1 H, C=CH], and 6.9–7.2 (m, 4 H, C$_6$H$_4$); ir spectrum identical with that of 2-methylindene.[22] The mass spectrum shows nearly the same cracking pattern as 3-methylindene and the mass spectra of both indenes are similar to that of a mixture of methylindenes found in the literature.[23] These same products were isolated and identified from the SSPA reactions of butyrophenone, 1-phenyl-2-butanone, 4-phenyl-2-butanone, 1-phenyl-1-butyne, and 4-phenyl-1-butyne. 1-Methylindan was isolated and identified similarly from the SSPA reactions of 4-phenyl-1-butene and 1-phenyl-2-butene.

Pivalophenone was prepared by a reverse Grignard reaction[24] and subjected to the catalyst in the same manner as described previously. Benzene, 1-methylindan, and 1,2-dimethylindan were isolated by preparative glpc and identified by comparison of their ir and nmr spectra and glpc retention times with those of authentic samples. 1- and 2-methylnaphthalene were isolated as a 1:1 mixture and identified by comparison of their physical and spectral properties with those of an authentic 1:1 mixture. A distillation fraction, bp 110–125° (30 mm), yielded 3.87 g of 2,3-dimethylindene by preparative glpc: mp 9–10° (lit.[25] mp 11°); ir spectrum identical with that for 2,3-dimethylindene;[22] nmr $\delta_{TMS}^{CCl_4}$ 1.75 (s, 6 H, CH$_3$C=CCH$_3$), 2.81 (br s, 2 H, CH$_2$), and 7.05 [s (fine splitting), 4 H, C$_6$H$_4$].

3-Methyl-2-butanone was allowed to react with the catalyst, and the 2,3-dimethylindene product, obtained by preparative glpc, was dissolved in benzene and subjected to fresh catalyst. The products were analyzed by glpc and nmr, showing 28% conversion of the indene into the same products obtained from pivalophenone and 3-methyl-3-phenyl-2-butanone.

Registry No.—**3**, 3910-35-8; **4**, 2177-47-1; **7**, 767-60-2; **9**, 767-58-5; 1,1-dimethylindan, 4912-92-9; 2,3-dimethylindene, 4773-82-4.

(22) T. L. Yarboro, C. Karr, Jr., and P. A. Estep, *J. Chem. Eng. Data*, **6**, 421 (1961).

(23) American Petroleum Institute, "Catalog of Mass Spectral Data," Serial No. 1250, Project No. 44, Carnegie Institute of Technology, Pittsburg, Pa.

(24) J. Ford, C. Thompson, and C. Marvel, *J. Amer. Chem. Soc.*, **57**, 2619 (1935).

(25) G. Egloff, "Physical Constants of Hydrocarbons," Vol. IV, Reinhold Publishing Corp., New York, N. Y., 1947, p 48.

The Reduction–Methylation of Derivatives of 3-Buten-2-one[1a]

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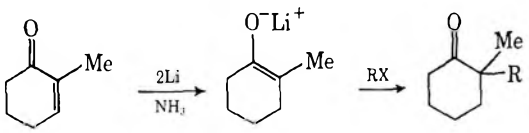
The lithium–liquid ammonia reduction and reduction–methylation of 3-buten-2-one derivatives *trans*-4-phenyl-3-buten-2-one (**1a**), 3-methyl-4-phenyl-3-buten-2-one (**1b**), and 4-methyl-3-penten-2-one (**1c**) have been investigated. In each case the only monomethylation product obtained was derived from the specific lithium enolate generated reductively. Unlike 2-cyclohexenone derivatives, open-chain enones **1a–1c** also gave much polymethylation, ascribed to the effect of the conjugate base of the proton donor employed in the reduction step. Polymethylation was minimized by the use of triphenylmethanol as proton donor or by the addition of excess acetone with the alkylating agent.

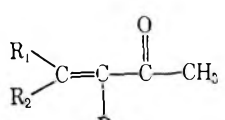
Stork and coworkers[2] have developed a procedure for the reduction–alkylation of an α,β-unsaturated ketone to give the α-alkyl saturated ketone uncontaminated with the α'-alkyl isomer. The procedure consists of treatment of an α,β-unsaturated ketone with 2 equiv of lithium in liquid ammonia to produce a specific lithium enolate, followed by treatment of the enolate with an alkyl halide in an appropriate solvent, as shown for 2-methyl-2-cyclohexenone in Scheme I.

SCHEME I



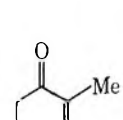
The specificity of the reduction–alkylation depends upon the relatively slow equilibration among structurally isomeric lithium enolates[2–6] and has been confirmed in several studies on reduction–alkylation in cyclic systems.[7–9]

Side reactions leading to polyalkylation products are generally moderate in extent for the reduction–alkylation of derivatives of 2-cyclohexenone[2,9] but extensive for systems in which the enone moiety is not part of a ring. In the present study, the reduction–methylation of some 3-buten-2-one derivatives (**1a–1c**) has been carried out with a view toward investigating the reaction pathway by which polymethylation occurs and finding optimum conditions for monomethylation. Some further work on cyclic systems has been carried out with 4,4-dimethyl-2-cyclohexenone (**1d**) and 2,4,4-trimethyl-2-cyclohexenone (**1e**).



1a, R_1 = Ph; R_2 = R_3 = H
b, R_1 = Ph; R_2 = H; R_3 = Me
c, R_1 = R_2 = Me; R_3 = H

1d



1e

(1) (a) Supported by the National Science Foundation and the Research Corporation. (b) Undergraduate Research Participant, National Science Foundation.

(2) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965).

(3) (a) R. E. Schaub and M. J. Weiss, *Chem. Ind.* (London), 2003 (1961); (b) R. Deghenghi and R. Gaudry, *Tetrahedron Lett.*, 489 (1962); (c) M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr., and C. J. Coscia, *Chem. Ind.* (London), 118 (1963); (d) R. Dehgenghi, C. Revesz, and R. Gandry, *J. Med. Chem.*, **6**, 301 (1963); (e) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964); (f) H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).

(4) D. Caine, *ibid.*, **29**, 1868 (1964).

(5) H. O. House and B. M. Trost, *ibid.*, **30**, 2502 (1965).

(6) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *ibid.*, **33**, 935 (1968).

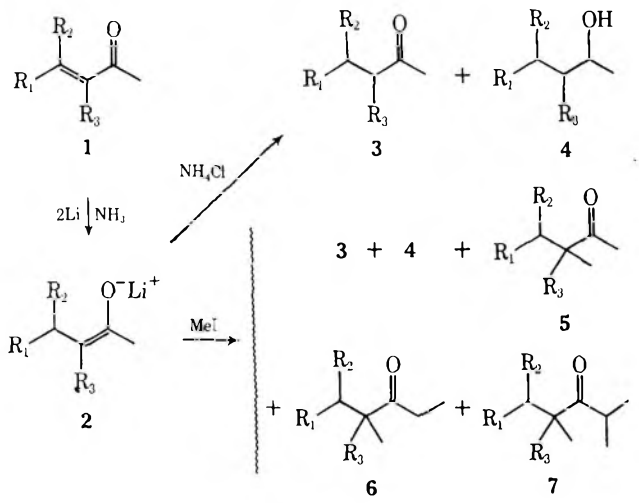
(7) D. Caine and B. J. L. Juff, *Tetrahedron Lett.*, 4695 (1966).

(8) D. Caine and B. J. L. Huff, *ibid.*, 3399 (1967).

(9) H. A. Smith, B. J. L. Huff, W. J. Powers, and D. Caine, *J. Org. Chem.*, **32**, 2851 (1967).

In order to establish that generation of the lithium enolates from **1** could be carried out in good yield, simple lithium–liquid ammonia reductions of enones **1a–1e** were performed. The enone (usually admixed with 1 equiv of a proton donor[9]) was added to 2 equiv of lithium in ammonia, followed by the addition of excess ammonium chloride to the mixture. The structures of the products isolated from enones **1a–1c** are shown in Scheme II, where **3** represents the α,β-dihydro product and **4** the saturated alcohol product in each case.

SCHEME II



Product analyses for the reduction experiments are shown in Table I. Every enone gave a satisfactory yield of **3**, either pure or containing no more than 7% of the saturated alcohol (**4**), when 1 equiv of *t*-butyl alcohol was added along with the enone. Significant quantities of alcohols have not been obtained in previous work on the reduction or reduction–alkylation of cyclic enones; in the present work they were likely formed by protonation of the enolate by the proton donor followed by further reduction by lithium. Smooth reduction to give **3** also resulted when triphenylmethanol was the proton donor; however, significant quantities (17–51%) of **4** were obtained with other donors. The extent of overreduction to give **4** does not correlate with the thermodynamic acidities of the donors.[10] However, such a correlation does obtain among the oxygen acid donors in Table I as well as between the nitrogen acid donors. It may be that the extent of overreduction depends upon the rate of attack of the donor on lithio carbanion aggregates and that initial coordination of nitrogen with lithium enhances the rate for nitrogen acids.

TABLE I
LITHIUM–LIQUID AMMONIA REDUCTIONS OF ENONES

Enone	Proton donor (1 equiv) used	Product composition, % 3	4	Yield, %
1a	*t*-BuOH	100	0	66[a]
1a	Ph_3COH	100	0	54[a]
1a	MeOH	83	17	
1b	*t*-BuOH	97	3[b]	61[a]
1c	*t*-BuOH	93[c]	7[c]	40,[a] 65[d]
1c	Ph_3COH	96	4	51[a]
1c	MeOH	78	22	
1c	Pyrrole	49	51	
1c	Ph_2NH	72	28	
1c	None	42	38[e]	
1d	*t*-BuOH	100	0	62[a]
1d	None	60	0[f]	
1e	Various[g]	100	0	97[d,h]
1e[i]	None	53	0[i]	

[a] Based on distilled material. [b] Not conclusively identified. [c] Average of two runs. [d] Based on vpc analysis using *m*-xylene as internal standard. [e] The product mixture also contained 20% starting enone **1c**. [f] The product mixture also contained 40% starting enone **1d**. [g] Separate trials gave the indicated product analysis with the following donors: acetic acid, water, pyrrole, *t*-butyl alcohol, diphenylamine, and triphenylmethane. [h] For trial using diphenylamine. [i] Data from ref 9. [j] The product mixture also contained 47% starting enone **1e**.

Previous work[9] has indicated that reduction of 2-cyclohexenones in the absence of a proton donor leads to recovery of significant quantities of starting enone, except with 3-methyl-2-cyclohexenone, which has a fully substituted β carbon. In contrast, Table I records that **1c**, which also has a fully substituted β carbon, gave 20% starting enone in the absence of a donor. It is noteworthy that **1e** was reduced smoothly to pure **3e** with a variety of proton donors, ranging from acetic acid ($pk = 5$) to triphenylmethane ($pk = 33$).[10] Conjugate addition by amide ion to form a reduction-resistant species has been suggested[9] to explain the recovery of enone in the reduction of **1e**; if so, it is interesting that even a proton donor so weakly acidic as triphenylmethane led to complete reduction of **1e**.

Results of Reduction–Methylation Experiments.—Reduction–methylations were carried out with compounds **1a–1d** by generating the enolate as described above for reduction and treating it with methyl iodide. An equal volume of ether was added before alkylation, as recommended previously.[9] The structures of the principal products (determined by spectroscopic techniques using samples collected by preparative-scale vpc) were as shown in Scheme II, where **5**, **6**, and **7** represent the mono-, di-, and trimethylation products, respectively. Each α,β-dihydro product (**3**) was identical with that produced by simple reduction. In addition, **5a**, the monomethylation product from **1a**, was identical with **3b**, the simple reduction product from **1b**; similarly, **5d** was identical with **3e**. In each case, the only monomethylation product (**5**) obtained was that derived from the specific enolate produced in the reduction step; *i.e.*, the α-methyl derivative was obtained but not the α'-methyl. This observation agrees with the established principle that the *lithium* enolates of ketones can be trapped by reactive alkylating agents without appreciable equilibration among the structurally isomeric enolates.[2–9]

Table II records the product analyses for some reduction–methylation experiments. Unlike substituted cyclohexenones[9] and other cyclic enones,[2] reduction–methylation of open-chain enones **1a–1c** gave rise to substantial quantities of polymethylation products (**6**, **7**), even when 1 equiv of methyl iodide was employed (Table II, expt 1, 2, and 8–10).

As a consequence of the proton donor employed in the reduction step, 1 equiv of the conjugate base of the donor (*e.g.*, lithium *t*-butoxide when *t*-butyl alcohol was

(10) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapter 1.

TABLE II

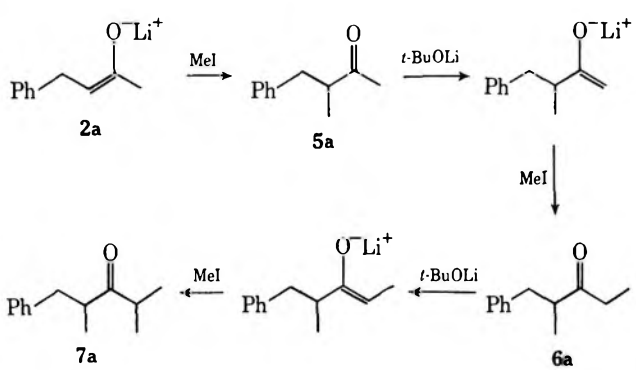
REDUCTION–METHYLATION OF ENONES IN ETHER–LIQUID AMMONIA

Expt	Enone	Proton donor (1 equiv) used	Equiv of compound added before methylation	Equiv of MeI	Product composition, % 3	4	5	6	7	Yield,[a] %
1[b]	1a	*t*-BuOH	...	1	23	0	54	16	7	66[c]
2	1a	*t*-BuOH	...	6	2	0	48	41	9	
3	1a	*t*-BuOH	1.0 *t*-BuOLi	6	1	0	13	20	66	
4	1a	Ph_3COH	...	6	20	0	73	7	0	69[d]
5	1a	Ph_3COH	0.5 Ph_3COLi	6	23	0	58	19	0	
6	1a	*t*-BuOH	1.0 **3d**[e]	6	5	0	50[f]	26	10	
7	1a	*t*-BuOH	...	24[g]	12	0	85	1	2	
8[b]	1b	*t*-BuOH	...	1	28	0	62	8[h]	2[h]	75[c]
9[b]	1c	*t*-BuOH	...	1	21	8	52	10	6[i]	79[c]
10[b]	1c	*t*-BuOH	...	3–5	1	9	34	33	23	
11	1c	Ph_3COH	...	3	9	7	75	8	0	84[d]
12	1d	*t*-BuOH	...	4	14	0	86	0	0	90[d]
13	1d	*t*-BuOH	1.0 **3a**[j]	6	10	0	90	0	0	
14[k]	1e	*t*-BuOH	...	6	7	0	93	0	0	46

[a] The total yield of all products, including starting material, is recorded. [b] Average of two runs. [c] Based on distilled material considering it to be only monoalkylation product. [d] Based on vpc analysis using *m*-xylene as internal standard. [e] 4,4-Dimethylcyclohexanone. Vpc indicated that 12% of **3d** was converted into 2,4,4-trimethylcyclohexanone (**5d**) in this experiment. [f] An unidentified product, 8%, with vpc retention time similar to that of **5** was detected. [g] Six equivalents of acetone added with MeI. [h] Not conclusively identified. [i] Vpc showed 3% unidentified high-boiling material. [j] Vpc indicated that 41% of **3a** had been converted into alkylation products in this experiment. [k] Data from ref 9.

the donor) was present during the alkylation step. A comprehensive study by House and Trost[5] of the alkylation of lithium enolates in 1,2-dimethoxyethane solution in the presence of lithium *t*-butoxide[11] indicated that this base was principally responsible for the polyalkylation they observed. In the present study, polymethylation products would be expected to result from the lithium alkoxide present during methylation, as depicted for the polymethylation of **2a** in Scheme III.

SCHEME III



Ancillary data on the effect of lithium alkoxides was provided by an investigation of the methylation of some saturated ketones in conditions similar to reduction–methylation experiments, and the results are recorded in Table III. The literature contains several examples of the alkylation of ketones in the presence of sodium or potassium alkoxides in solvents such as ethers, hydrocarbons, and alcohols,[12] but the use of lithium alkoxides in ammonia has not been reported.

Each of the open-chain saturated ketones **3a–3c** underwent substantial mono- and dimethylation in ether–ammonia when treated with 1 equiv of lithium

(11) One equivalent lithium *t*-butoxide was produced as a consequence of the reaction by which specific enolates were generated by these workers: the treatment of 1 equiv of an enol acetate with 2 equiv of methyllithium.

(12) See H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 184–189.

TABLE III

METHYLATION[a] OF KETONES IN ETHER–LIQUID AMMONIA USING LITHIUM *t*-BUTOXIDE

Ketone	Product composition, % Starting material	Monomethylation product	Dimethylation products
3a[b]	50	43[c]	7[d]
3b (**5a**)[e,f]	43	46[g]	11[h]
3c	24	58[i]	18[j]
3c[k]	45	55	0
3d	70	30[l]	0
3e (**5d**)[m]	75	25[n]	0

[a] Unless otherwise indicated, 6 equiv of MeI and 1 equiv of *t*-BuOLi were employed in each experiment. [b] Total ketone recovery was 65% using *m*-xylene internal vpc standard. [c] Probably 1-phenyl-3-pentanone. [d] Mixture of two components believed to be isomeric dimethylation products. [e] Average of two runs. [f] Total ketone recovery was 70% using *m*-xylene internal vpc standard. [g] Identical with **6a**. [h] Identical with **7a**. [i] 5-Methyl-3-hexanone. [j] Mixture of three or more components; major component 2,5-dimethyl-3-hexanone. [k] Lithium amide was employed as base in this experiment. [l] 2,4,4-Trimethylcyclohexanone. [m] Four equivalents of MeI were employed in this experiment. [n] 2,4,4,6-Tetramethylcyclohexanone.

t-butoxide followed by excess methyl iodide. The methylation products in each case were those derived from successive replacement of hydrogen at the *less* highly substituted α carbon. The methylation of **3b** was particularly noteworthy in that the starting material was identical with **5a**, the monomethylation product in reduction–methylation of **1a** (Table II, expt 2). The higher methylation products had identical structures in the two experiments. Although methylation could also be carried out using lithium amide (see Table III), the presence of this base during reduction–methylation is ruled out by the presence of the proton donor, an acid much stronger than ammonia. Also, lithium amide forms a suspension in ether–ammonia, whereas homogeneous mixtures were observed in reduction–methylation.

Further evidence for the effect of lithium *t*-butoxide was obtained by the addition of an equimolar amount of that compound (thus doubling its concentration)

to **2a** before methylation (Table II, expt 3). A substantial increase in total polymethylation products resulted (*cf.* expt 2). The increase in the *extent* of polymethylation was greater than indicated by a simple comparison of percentages, since the trimethylation product (**7a**) (66% in expt 2) was derived from a monomethylation product which had been alkylated two additional times.

In an effort to find an effective proton donor whose conjugate base would cause less polymethylation, triphenylmethanol was employed (Table II, expt 4 and 11). Much less polymethylation resulted (*cf.* expt 2 and 10) and a good yield of relatively pure **5** was obtained. The addition of lithium triphenylmethoxide before methylation (expt 5) increased polymethylation, but not as much as *t*-butoxide.

Triphenylmethanol is the reagent of choice as proton donor in reduction–methylation syntheses, based on its effect in promoting effective reduction and minimizing polymethylation. The lower extent of polymethylation may be due to steric factors, the base strength of triphenylmethoxide, or aggregation of lithium triphenylmethoxide.

It is possible that part of the polymethylation comes as a result of ionization of ketonic products (*e.g.*, **5**) by unreacted enolate **2**. This proton-transfer reaction would result in formation of the α,β-dihydro product **3**, which was indeed obtained in each reduction–methylation experiment. Direct evidence against appreciable proton transfer of this type came from expt 6 and 13 of Table II, in which an equimolar quantity of a structurally dissimilar, saturated ketone was added to enolate **2** *before* methylation. No appreciable increase in the proportion of **3** compared with control experiments (expt 2 and 12) was found. It seems likely that **3** arose, as suggested previously,[9] from protonation of **2** by methylammonium ion derived from methyl iodide solvolysis. This view is supported by an experiment in which methyl iodide was stirred in liquid ammonia for 15 min and then added to a solution of enolate **2e**. No methylation products were detected and 79% **3e** was obtained.

The failure to observe appreciable enolate equilibration suggested a procedure to minimize polymethylation. A large excess of methyl iodide admixed with excess acetone was added to enolate **2a** (Table II, expt 7). The monomethylation product (**5a**) comprised 85% of the product mixture, total polymethylation amounted to only 3%, and only a moderate quantity of **3a** (12% compared with 2% in expt 2) was obtained.

The structures of the methylation products obtained in the experiments of Tables II and III indicates that each is derived from the less highly substituted *kinetic* enolate.[4,13] The failure to observe substantial amounts of products derived from the more highly substituted enolates[14] suggests that lithium alkoxides may be more selective kinetically than trityllithium previously employed.[4,13]

The extent of polymethylation in the open-chain ketones investigated here is greater than in alicyclic ketones because the kinetic acidity of the former is greater. The possibility that alicyclic ketones are thermodynamically less acidic and do not transfer a proton to alkoxides in ammonia is eliminated by the successful methylation of **3d** and **3e** using lithium *t*-butoxide (Table III). Modest differences in the extent of polymethylation have previously been observed in the reduction–methylation of substituted 2-cyclohexenones.[9] The differences can probably be ascribed to slight differences in the kinetic acidities of the ketonic products.

(13) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

(14) Kinetic studies[7,8] have shown comparable alkylation rates for structurally isomeric lithium enolates derived from cyclohexanones.

Experimental Section[15]

trans-**4-Phenyl-3-buten-2-one** (**1a**), **4-methyl-3-penten-2-one**[16] (**1c**), **4-methyl-2-pentanone** (**3c**), **and 4-methyl-2-pentanol** (**4c**) were commercial products.

2,4,4-Trimethyl-2-cyclohexenone (**1e**), bp 85–88° (20 mm), **2,4,4-trimethylcyclohexanone** (**3e**), bp 82° (20 mm), and **4,4-dimethyl-2-cyclohexenone** (**1d**), bp 79–80° (20 mm), were prepared as previously described.[9]

3-Methyl-4-phenyl-3-buten-2-one (**1b**) gave the following data: bp 117° (5 mm) [lit.[17] bp 130° (12 mm)]; ir 6.00 and 6.14 μ; nmr δ 1.82 (d, 3, J = 1 Hz, C-3 Me), 2.16 (s, 3, C-1 Me), 6.78 (s), and 6.81 (d, J = 1 Hz), total area 6 (C_6H_5 and —CH=, respectively). This compound was prepared in 58% yield by published methods.[18]

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.36; H, 7.49.

Lithium *t*-butoxide was prepared by refluxing lithium metal with excess *t*-butyl alcohol (freshly distilled from sodium) and evaporating the excess alcohol *in vacuo* at 70°. Lithium triphenylmethoxide was prepared by treating triphenylmethanol in hexane under N_2 with *n*-butyllithium in hexane, heating to reflux, and distilling two-thirds of the solvent. The product was collected by suction filtration and dried *in vacuo*.

General Procedure for Lithium–Liquid Ammonia Reduction of Enones.—The reductions of the various α,β-unsaturated ketones were carried out as described previously[9] by adding dropwise under N_2 over a 20–30-min period an equimolar mixture of enone and proton donor in three volumes of ether to a stirred solution of *ca.* 2.2 g-atoms of lithium/1 mol of ketone in dry ammonia (distilled from sodium, *ca.* 0.5–1 ml per 1 mg of lithium). The reaction mixture usually remained blue; occasionally the blue color was discharged after *ca.* 90% of the enone was added, in which case the addition was stopped. The mixture was stirred for 20–30 min and excess NH_4Cl was added. After evaporation of the ammonia at room temperature and reaction mixture was worked up as before[9] in water and ether. The combined ether extracts were dried and concentrated to a small volume under reduced pressure. Vpc analysis[19] was carried out at this point; a weighed quantity of *m*-xylene was added to some product mixtures as an internal standard. In some trials, no internal standard was added and distillation was carried out after vpc analysis. In the reductions of **1c**, only about two-thirds of the ether was removed under reduced pressure; the remainder was taken off at atmospheric pressure by flash distillation through a 1 × 30 cm unpacked column.

(15) Melting points, determined on a Fisher-Johns apparatus, and boiling points were uncorrected. Ir spectra were determined with a Perkin-Elmer 137b spectrophotometer. Nmr spectra were determined at 60 MHz with a Varian A-60 spectrometer and unless otherwise stated are in CCl_4 solution relative to internal TMS. Analytical vpc was performed on an F & M Model 700 gas chromatograph with helium as the carrier gas. Product composition was calculated by the area normalization method. Preparative vpc was performed on a Microtek 2500R with nitrogen as the carrier gas. *t*-Butyl alcohol was refluxed over sodium and distilled. Methyl alcohol was distilled from magnesium methoxide. Acetic acid was distilled from acetyl borate. Pyrrole was dried over potassium hydroxide. Triphenylmethanol, diphenylamine, and triphenylmethane were used as received. Methyl iodide was distilled from phosphorus pentoxide. All ketone starting materials were distilled and were at least 99% pure by vpc. Lithium metal wire was a low-sodium product from Lithium Corp. of America. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

(16) Dried over Drierite and distilled using a spinning-band column.

(17) I. Heilbron, Ed., "Dictionary of Organic Compounds," Vol. IV, 4th ed, Oxford University Press, New York, N. Y., 1965, p 2294.

(18) (a) M. T. Bogert and D. Davidson, *J. Amer. Chem. Soc.*, **54**, 335 (1932); (b) J. D. Gettler and L. B. Hammett, *ibid.*, **64**, 1826 (1942).

(19) Unless otherwise noted, vpc analyses were carried out using a column packed with SE-30 silicone gum rubber.

Reductions of *trans*-4-Phenyl-3-buten-2-one (1a).—From 14.6 g (0.1 mol) of **1a**, 7.41 g (0.1 mol) of *t*-BuOH, and 1.60 g (0.23 g-atom) of lithium in 500 ml of ammonia was obtained 9.76 g (66%) of pure 4-phenyl-2-butanone (**3a**): bp 80–85° (8 mm) [lit.[20] bp 115° (13 mm)]; ir 5.83 μ; nmr δ 1.93 (s, 3), 2.34–3.00 (br, 4), and 7.12 (s, 5).

Anal. Calcd for $C_{10}H_{1}O_2$: C, 81.04; H, 8.16. Found: C, 81.15; H, 8.10.

In a similar run using MeOH as the proton donor, vpc analysis indicated that the product mixture consisted of 83% **3a** and 17% **4a**, identified by vpc retention time.

Reduction of 3-Methyl-4-phenyl-3-buten-2-one (1b).—From 12.6 g (0.079 mol) of **1b**, 5.84 g (0.079 mol) of *t*-BuOH, and 1.22 g (0.18 g-atom) of lithium in 1000 ml of ammonia was obtained 7.69 g (61%) of 3-methyl-4-phenyl-2-butanone (**3b**): bp 78–79.5° (1 mm) [lit.[18a] bp 127–130° (12 mm)]; ir 5.85 μ; nmr δ 0.91 (d, 3, *J* = 5.5 Hz, C-3 Me), 1.78 (s, 3, C-1 Me), 2.17–2.78 (br, 3), and 6.52 (s, 5). Vpc analysis indicated the presence of 3% of an impurity whose retention time was that expected for **4b**.

Anal. Calcd for $C_{11}H_{14}O$: 81.44; H, 8.70. Found: C, 81.26; H, 8.77.

Reductions of 4-Methyl-3-penten-2-one (1c).—From 9.82 g (0.1 mol) of **1c**, 7.42 g (0.1 mol) of *t*-BuOH, and 1.68 g (0.24 g-atom) of lithium in 500 ml of ammonia was obtained 3.98 g (40%) of material, bp 110–114°. Vpc analysis of the crude mixture indicated that it consisted of 94% 4-methyl-2-pentanone (**3c**) and 6% 4-methyl-2-pentanol (**4c**). The ir spectrum of the product was identical with that of authentic **3c** except for a small hydroxylic absorption at 2.85 μ. The vpc retention times of both **3c** and **4c** were identical with those of authentic compounds.

Additional runs were carried out with other proton donors, using *ca.* 2 g of enone and 400 ml of ammonia. In a run in which no donor was used, the product mixture contained 20% of starting enone **1c**, identified by vpc retention time.

Reductions of 4,4-Dimethyl-2-cyclohexenone (1d).—From 5.14 g (0.41 mol) of **1d**, 3.31 g (0.45 mol) of *t*-BuOH, and 0.65 g (0.94 g-atom) of lithium in 500 ml of ammonia was obtained 3.12 g (62%) of pure 4,4-dimethylcyclohexanone (**3d**), bp 88–91° (45 mm) [lit.[21] bp 73° (14 mm)], ir 5.83 μ.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.08; H, 11.11.

In a run in which no proton donor was added, the product mixture consisted of 60% **3d** and 40% starting enone **1d**, identified by vpc[22] retention times.

General Procedure for Reduction–Methylation of Enones.—The reduction step was carried out by the same general procedure described for the reduction runs. Approximate solubility measurements indicated limited solubility for lithium enolates and lithium *t*-butoxide in ammonia at −33°; however, the solubilities were greater in ether. Therefore, after 20–30 min of stirring the enolate mixtures were generally diluted with an equal volume of dry ether. The blue color was discharged during the addition. The enolate mixtures in ammonia usually contained suspended white solid material; the material dissolved when ether was added and clear, apparently homogeneous mixtures resulted. For the alkylation step, MeI (usually 6 equiv/mol of ketone used) in three volumes of ether was added dropwise with stirring over 10–20 min. The ammonia was allowed to evaporate at room temperature, and the reaction mixture was worked up in a manner identical with that described for the reduction runs. Vpc analysis was carried out after removal of most of the solvent but before distillation. In duplicate runs, the percentages of a given component generally agreed within 5%. In some runs a final distillation was carried out to obtain the yield of distillable material; yields were obtained in other runs by use of *m*-xylene as an internal standard for vpc analysis. Product analyses for various runs are recorded in Table II.

Reduction–Methylations of *trans*-4-Phenyl-3-buten-2-one (1a).—From 14.6 g (0.1 mol) of **1a**, 7.41 g (0.1 mol) of *t*-BuOH, 1.53 g (0.22 g-atom) of lithium in 600 ml of ether–ammonia, and 14.2 g (0.1 mol) of MeI was obtained 11.6 g (66% yield, assuming product to be only **5a**) of a mixture of ketones, bp 94–97° (3 mm), with the following composition: **3a**, 24%; **5a**, 55%; **6a**, 14%; and **7a**, 5%. In a similar run on *ca.* one-fifth the scale in 500 ml of ammonia, the product analysis was as follows: **3a**, 22%; **5a**, 52%; **6a**, 16%; and **7a**, 11%. The components were collected by preparative vpc, and (in order of elution) were identified as follows: **3a**, 4-phenyl-2-butanone, ir and nmr spectra and vpc retention time identical with those of **3a** from reduction runs; **5a**, 3-methyl-4-phenyl-2-butanone, ir and nmr spectra and vpc retention time identical with those of **3b** from reduction of **1b**; **6a**, 2-methyl-1-phenyl-3-pentanone, ir 5.83 μ, nmr δ 0.90 (t, *J* = 6 Hz) and 1.03 (d, *J* = 5 Hz), total area 6 (C-5 and C-2 Me, respectively), 1.92–3.03 (br, 5), and 7.13 (s, 5), 2,4-dinitrophenylhydrazone mp 94–95° (lit.[23] mp 95–96°). The nmr spectrum indicated small quantities (<10%) of another compound, which was probably an isomer of **6a**. Compound **7a** was eluted last, and although the spectral data were not conclusive in this case, the structure most consistent with the data was 2,4-dimethyl-1-phenyl-3-pentanone: ir 5.83 μ; nmr δ 0.80 (d, *J* = 7 Hz), 0.97 (d, *J* = 7 Hz), 9.04 (d, *J* = 6.5 Hz) (total area 0.70–1.20, 9), 1.91–3.17 (br, 4), and 7.13 (s, 5).

In expt 3 and 5, Table II, lithium alkoxide was added after generation of the enolate in the usual manner. The mixture was stirred for 10 min before addition of MeI.

In expt 6, Table II, 1 equiv of 4,4-dimethylcyclohexanone (**3d**) was added to the enolate mixture, followed immediately by MeI. An unidentified compound, 8% of the total material derived from **1a**, eluted between **3a** and **5a** upon vpc analysis. Of the material derived from **3d**, 88% was recovered **3d** and 12% was **5d**.

In expt 7, Table II, a mixture of 6 equiv of dry acetone and 24 equiv of MeI was added as rapidly as possible to the enolate generated from **1a**.

Reduction–Methylations of 3-Methyl-4-phenyl-3-buten-2-one (1b).—From 16.0 g (0.1 mol) of **1b**, 7.41 g (0.1 mol) of *t*-BuOH, 1.53 g (0.22 g-atom) of lithium in 600 ml of ether–ammonia, and 14.2 g (0.1 mol) of MeI was obtained 10.6 g of material, bp 101–110° (6 mm). The blue color was discharged after 80% of **1b** had been added and the addition was stopped. The yield was 75%, based upon the quantity of **1b** added and assuming the mixture to consist of only **5b**. The major components of the product mixture were collected by preparative vpc and were identified as follows (in order of elution): **3b**, 2-methyl-4-phenyl-2-butanone, ir spectrum and vpc retention time identical with those of **3b** obtained in reduction runs; **5b**, 3,3-dimethyl-4-phenyl-2-butanone, ir 5.83 μ, nmr δ 1.07 (s, 6, CMe_2), 1.99 (s, 3, COMe), 2.74 (s, 2, $PhCH_2$), and 7.13 (s, 5). Compounds **6b** and **7b** were not isolated but gave vpc retention times expected for di- and trimethylation products. The crude product composition was as follows: **3b**, 35%; **5b** 57%; **6b**, 7%; and **7b**, 1%. In a similar run the composition was as follows: **3b**, 21%; **5b**, 67%; **6b**, 10%; and **7b**, 2%.

Reduction–Methylations of 4-Methyl-3-penten-2-one (1c).—From 9.82 g (0.1 mol) of **1c**, 7.41 g (0.1 mol) of *t*-BuOH, 1.53 g (0.22 g-atom) of lithium in 800 ml of ether–ammonia, and 14.2 g (0.1 mol) of MeI was obtained 9.1 g (79%, assuming the mixture to be only **5c**) of distilled material. The major components of the product mixture were collected by preparative vpc and identified as follows (in order of elution): **3c**, 4-methyl-2-pentanone, vpc retention time identical with that of **3c** from reduction runs; **4c**, 4-methyl-2-pentanol, ir 2.95 μ, nmr δ 0.91 (d, 6, *J* = 6 Hz), 1.14 (d, 3, *J* = 6 Hz), 1.67–2.34 (br, 3), 3.79 (br, 1, CHOH), and 4.77 (br s, 1, OH), vpc retention time identical with that of authentic **4c**; **5c**, 3,4-dimethyl-2-pentanone, ir 5.83 μ, nmr δ 0.84 (d, *J* = 6.5 Hz), 0.90 (d, *J* = 6 Hz), 0.98 (d, *J* = 6.5 Hz) (total area 0.70–1.10, 9), 2.05 (s, 3), 1.61–2.53 (br, 2), 2,4-dinitrophenylhydrazone mp 94.5–95.5° (lit.[24] mp 94–95°); **6c**, 4,5-dimethyl-3-hexanone, ir 5.83 μ, nmr δ 0.83 (d, *J* = 6.5 Hz), 0.90 (t, *J* = 6.5 Hz), 0.91 (d, *J* = 7 Hz), 1.01 (d, *J* = 7.5 Hz) (total area 0.70–1.20, 12), 1.50–2.60 (br, 2), and 2.40 (q, *J* = 7.5 Hz). The nmr spectrum was nearly identical with that of **5c** in the δ 1.0 region except for the triplet at δ 0.90. The nmr spectrum is clearly consistent with the postulated structure and inconsistent with 3,3,4-trimethyl-2-pentanone, which would result from methylation of **5c** at the more highly substituted α position. Compound **7c**, 2,4,5-trimethyl-3-hexanone, was eluted

(20) I. Heilbron, Ed., "Dictionary of Organic Compounds," Vol. IV, 4th ed, Oxford University Press, New York, N. Y., 1965, p 2675.

(21) I. Heilbron, Ed., "Dictionary of Organic Compounds," Vol. II, 4th ed, Oxford University Press, New York, N. Y., 1965, p 1163.

(22) A Carbowax 20M column was used; SE-30 did not separate **1d** and **3d**.

(23) R. Jacquier, *Bull. Soc. Chim. Fr.*, 1653 (1956); *Chem. Abstr.*, **51**, 8023e (1958).

(24) A. P. Meshcheryakov and L. V. Petrov, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 1057 (1955); *Chem. Abstr.*, **50**, 11239f (1956).

next: ir 5.83 μ; nmr δ 0.70–1.15 (complex set of sharp peaks, 15), *ca.* 1.80 (m, 1, J = 7 Hz), and *ca.* 2.40 (m, 2, J = 7 Hz). The nmr spectrum is clearly consistent with the postulated structure. The alternative structure, 4,4,5-trimethyl-3-hexanone, which would result from methylation of **6c** at the more highly substituted α position, is inconsistent in that it requires a quartet centered at *ca.* δ 2.40; the spectrum has a clear multiplet of at least sixth order in this region. The crude product composition follows: **3c**, 24%; **4c**, 5%; **5c**, 53%; **6c**, 11%; **7c**, 4%; and unidentified high-boiling material, 4%. A similar run on a smaller scale gave the following composition: **3c**, 17%; **4c**, 11%; **5c**, 51%; **6c**, 9%; **7c**, 7%; and unidentified high-boiling material, 3%.

Reduction–Methylations of 4,4-Dimethylcyclohex-2-enone (1d).—From 2.00 g (0.016 mol) of **1d**, 1.197 g (0.016 mol) of *t*-BuOH, 0.255 g (0.037 g-atom) of lithium in 750 ml of ether–ammonia, and 9.0 g (0.06 mol) of MeI was obtained 0.89 g (45% assuming the product to be only **5d**) of material, bp 75–85° (40 mm). Analysis by vpc[25] gave a composition of 30% **3d** and 70% **5d**, identified by comparison of retention times with those of authentic compounds from reduction runs.

In another run, the enolate was generated as usual from 1.243 g (0.01 mol) of **1d**, 0.741 g (0.01 mol) of *t*-BuOH, and 0.152 g (0.022 g-atom) of lithium in 800 ml of ether–ammonia. 4-Phenyl-2-butanone (**3a**), 1.485 g (0.01 mol), was added to the stirred mixture followed immediately by 8.52 g (0.06 mol) of MeI. For the material derived from **1d**, vpc analysis gave the following composition: **3d**, 10%; **5d**, 90%. For the material derived from **3a**, vpc analysis gave the following composition: **3a**, 59%; and two later eluting components, 38 and 3%. These two components gave vpc retention times similar, but not identical, with those of **5a** and **6a** and were probably isomeric mono- and dimethylation products.

Methylation of Saturated Ketones.—The saturated ketone in three volumes of ether was added dropwise with stirring over 10 min to a solution of *t*-BuOLi in 1:1 ether–ammonia under N_2. The mixture was stirred for 10 min and MeI in three volumes of ether was added dropwise over 5 min. After 15 min, excess NH_4Cl was added and the mixture was worked up and analyzed as usual. The methylation of **3a** gave a monomethylation product with a vpc retention time similar but not identical with that of **5a**, probably the isomeric compound 1-phenyl-3-pentanone. The major dimethylation product had a vpc retention time identical with that of **6a**. Compounds **3d** and **3e** gave 2,4,4-trimethylcyclohexanone and 2,4,4,6-tetramethylcyclohexanone, respectively, with vpc retention times identical with those of authentic materials. Compound **3b** (**5a**) gave a mixture of three components which were collected by vpc and shown to be **5a**, **6a**, and **7a** by comparison of ir and nmr spectra with those of material from reduction–methylation runs. Compound **3c** gave a mixture of four or more methylation products. The two major components were collected by vpc and assigned structures as follows: 5-methyl-3-hexanone, nmr δ 0.90 (d, 6, J = 6 Hz, $CHMe_2$), 0.99 (t, 3, J = 7.5 Hz, CH_2CH_3), 2.22 (d, 2, J = 2 Hz, $CHCH_2$), *ca.* 2 (br, CH), and 2.33 (q. 2, J = 7.5 Hz, CH_2CH_3); and 2,5-dimethyl-3-hexanone, nmr 0.90 (d, 6, J = 6 Hz, CMe_2), 1.03 (d, 6, J = 6.5 Hz, CMe_2), 2.23 (d, 2, J = 2 Hz, CH_2), and *ca.* 2–2.5 (br, 2, CH).

Registry No.—**1a**, 1896-62-4; **1b**, 1901-26-4; **1c**, 141-79-7; **4c**, 108-11-2; **5b**, 13705-37-8; **5c**, 565-78-6; **6a**, 23936-95-0; **6c**, 6137-14-0; **7a**, 23936-97-2; **7c**, 23936-98-3; 5-methyl-3-hexanone, 623-56-3; 2,5-dimethyl-3-hexanone, 1888-57-9.

Acknowledgment.—We are grateful to Professor Drury Caine of Georgia Institute of Technology for helpful discussions and for obtaining some of the nmr spectra.

(25) An Apiezon L column was used for the analysis. A second analysis on Carbowax 20M indicated the absence of starting material (**1d**).

On the Conformation of *endo*-Bicyclo[3.3.1]nonan-3-ol. A New Synthesis of Oxaadamantane

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The results of spin-decoupling and variable-temperature nmr studies show a conformational equilibrium to be occurring in *endo*-bicyclo[3.3.1]nonan-3-ol. From the magnitude of the coupling constants, it is concluded that the major conformer is the chair–boat form. On the basis of a facile radical oxidation of the alcohol to the bridged ether, oxaadamantane, it is suggested that the minor conformer is the chair–chair form.

Transannular reactions commonly observed in medium-ring compounds have been widely studied, and generally interpreted on the basis of proximity effects.[2] As part of a continuing investigation on transannular radical and carbenoid reactions,[3] we have examined the bicyclo[3.3.1]nonane system, a potentially interesting homolog of cyclooctane.

In cyclooctane itself, the theoretically most stable conformation is the boat–chair, **1**.[4] Calculations also show that the crown form, **2**, and slightly modified

1 **2** **3**

forms thereof are somewhat disfavored relative to **1**, the differences in energy content being small and on the order of 2–3 kcal/mol.[4] Another conformer, **3**, is easily excluded in all calculations owing to the nonbonded interactions between the *endo* hydrogens. These theoretical conclusions have been supported by

(1) (a) To whom inquiries should be addressed. (b) Chargé de Recherches au CNRS; Boursier de l'OTAN, 1968–1969.

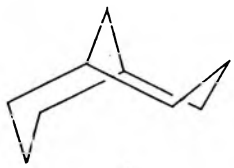
(2) For a recent review, see A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.* (London), **20**, 119 (1966).

(3) M. H. Fisch and H. D. Pierce, Jr., *J. Chem. Soc., D*, in press.

(4) (a) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **86**, 4854 (1964); (b) K. B. Wiberg, *ibid.*, **87**, 1070 (1965); (c) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *ibid.*, **90**, 1199 (1968); (d) M. Bixon, and S. Lifson, *Tetrahedron*, **23**, 769 (1967).

X-ray data on cyclooctane-1,2-*trans*-dicarboxylic acid, which is shown to exist in the boat–chair form.[5a] Elegant nmr studies extend this conclusion to cyclooctane and alkylcyclooctanes in solution.[5b]

If one attaches a methylene bridge from C-1 to C-5, the bicyclononane system is generated, and the derived conformers **4**–**6** may now be considered. Both **4** and **5** are destabilized relative to their cyclooctane analogs, **1** and **2**, by the interactions associated with cyclohexane boats. As a result, **6** is calculated to be the most stable conformer despite the interactions between the *endo* hydrogens at C-3 and C-7. The energy content of **6** is estimated to be 2.7 kcal/mol less than that of the second most stable conformer, **4**. Crystallographic data support the assignment of the parent molecule as chair–chair,[6] and have stimulated a variety of investigations on the ease of ionic transannular reaction involving C-3 and C-7.[7]



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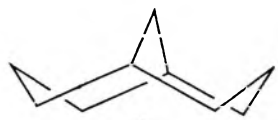

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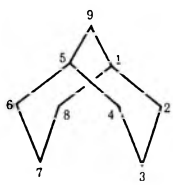
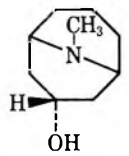


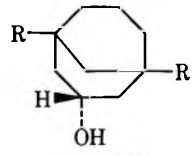
6

There is thus a delicate balance in the parent hydrocarbon between forms **4** and **6** in which the latter predominates. The main destabilizing factors in **6** are nonbonded repulsions (*ca.* 2 kcal/mol), torsional strain, and angle strain (at least 2 kcal/mol).[8] These destabilizing factors are aggravated without greatly affecting alternate conformer **4** by *endo* substituents at C-3. Hence, appropriate substitution could conceivably shift the conformational preference to favor the chair–boat form, **4**, in analogy with cyclooctane. Certainly, one might anticipate such a shift if the substituent were large, *e.g.*, methyl. On the other hand, substitution of hydroxyl, a group of intermediate size and one of immediate interest to us, does not lead to a clear-cut situation.

Chen and Le Fevre[9] and Parker, *et al.*,[10] have concluded from a first-order analysis of the nmr pattern corresponding to the carbinyl proton, CHOH, that the major conformer is analogous to the chair–boat form, **4**, in 3α-granatanol[9] (**7**) and in *endo*-1,5-dimethylbicyclo[3.3.1]nonan-3-ol[10] (**8a**), respectively. In the same way, Flegal reached an analogous conclusion for the parent alcohol, **8b**.[11]



7



8a, R = CH_3
b, R = H

These interpretations, based on first-order analyses, are neither completely satisfying nor entirely unambiguous. If a rapid conformational equilibrium is present, the coupling constants observed between the carbinyl and vicinal protons will be weighted averages, and, without appropriate models for the chair–boat form, one cannot calculate how important the chair–chair conformer might be, or even whether the chair–chair form is present. Thus, whereas Chen and Le Fevre estimated that 14% of **7** exists in the chair–chair form at room temperature,[9] Parker suggested that it would be more prudent to reserve judgment.[10] Indeed, he showed that direct application of the method used by Chen and Le Fevre to the case of **8a** would result in an estimate of considerably more than 100% chair–boat conformer.

One may question also the validity of a direct first-order analysis in extracting the coupling constants for the present AA′BB′X systems, although it turns out that the true values are not greatly different (see below).

The only other data relevant to the conformational preferences of these systems comes from the application of a semiempirical infrared method to the case of 3α-granatanol (**7**).[12] The conclusion, based on shapes and frequencies of the OH bands in the two epimeric alcohols, was that the chair–chair form analogous to **6** is preferred in the *endo* isomer. Noting that this result was counter to the previous nmr studies, Aaron, *et al.*, commented that their results did not constitute absolute proof in the absence of an appropriate model for the chair–boat form, but did show that the chair–chair form was certainly not to be excluded, and that further studies were clearly needed.

Results and Discussion

Faced with this situation, we sought to answer three questions: (A) is there a conformational equilibrium between chair–boat and chair–chair forms; (B) if so, what is the major conformer; (C) is it possible to direct transannular chemistry through a chair–chair form such as **9a**, and, in particular, to obtain oxaadamantane (**10**) by treatment of **8b** with radical oxidants?

Synthesis of the parent alcohol, *endo*-bicyclo[3.3.1]-nonan-3-ol (**8b**), is described in the Experimental Section. The nmr pattern of the carbinyl proton,

(5) (a) J. D. Dunitz and A. Mugnoli, *Chem. Commun.*, 166 (1966); (b) F. A. L. Anet and M. St. Jacques, *J. Amer. Chem. Soc.*, **88**, 2585, 2586 (1966).

(6) (a) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); (b) W. A. C. Brown, C. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); (c) W. A. C. Martin, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965); (d) I. Laszlo, *Rec. Trav. Chim. Pays-Bas*, **84**, 251 (1965).

(7) (a) R. A. Appleton and S. H. Graham, *Chem. Commun.*, 297 (1965); (b) R. A. Appleton, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 805 (1967); (c) H. Stetter, J. Gartner and P. Tacke, *Angew. Chem. Int. Ed. Engl.*, **4**, 153 (1965); (d) M. Eakin, J. Martin, and W. Parker, *Chem. Commun.*, 206 (1965), 955 (1967), and 298 (1968); (e) H. Dugas, R. A. Ellison, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Lett.*, 1279 (1965); (f) W. A. Ayer and K. Piers, *Chem. Commun.*, 541 (1965); (g) J. P. Schaefer and C. A. Flegal, *J. Amer. Chem. Soc.*, **89**, 5729 (1967); (h) M. A. Eakin, J. Martin, W. Parker, C. Egan, and S. H. Graham, *Chem. Commun.*, 337 (1968).

(8) G. J. Gleicher and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967).

(9) C. Y. Chen and R. J. W. Le Fevre, *Tetrahedron Lett.*, 737 (1965); *J. Chem. Soc., B*, 539 (1966).

(10) W. D. K. Macrossan, J. Martin, and W. Parker, *Tetrahedron Lett.*, 2589 (1965).

(11) C. A. Flegal, Ph.D. Thesis, University of Arizona, 1968, p 7 ff.

(12) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967); see also L. Joris, P. von R. Schleyer, and E. Osawa, *Tetrahedron*, **24**, 4759 (1968).

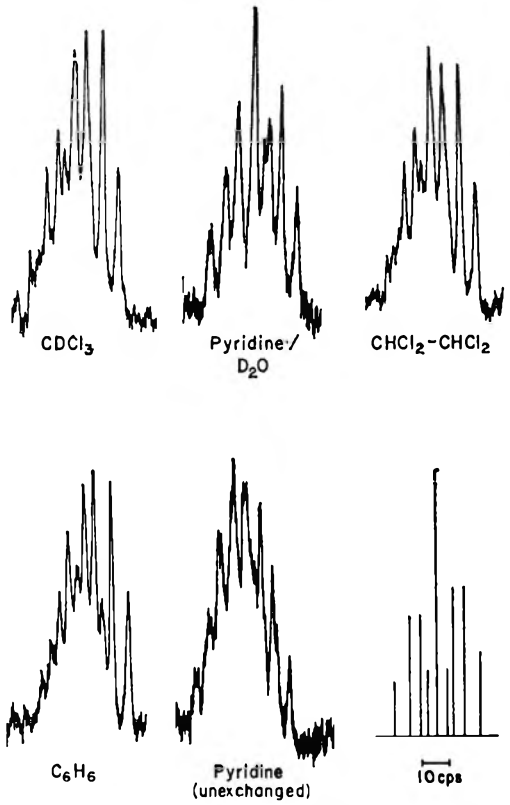
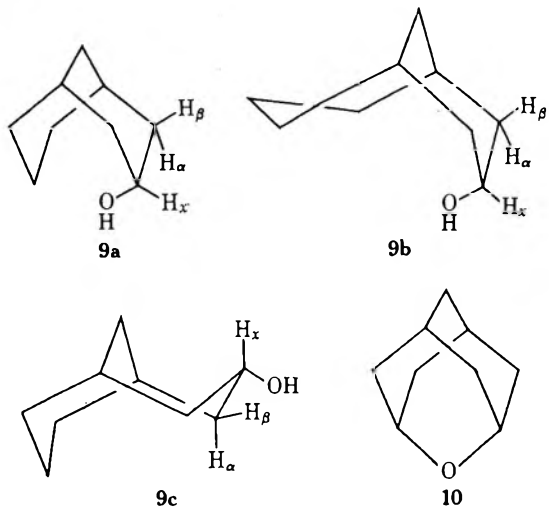


Figure 1.—Experimental and calculated spectra of the carbinyl proton of *endo*-bicyclo[3.3.1]nonan-3-ol (60 MHz).

CHOD, following exchange of the hydroxyl hydrogen, is shown in various solvents in Figure 1. For comparison, a calculated spectrum (LAOCOON 3) for H_x is also shown, based on the coupling constants $J_{H_\alpha H_x}$ = 10.0 cps and $J_{H_\beta H_x}$ = 6.2 cps, with chemical shifts δ_{H_α} = 70 cps, δ_{H_β} = 123 cps, and δ_{H_x} = 246 cps relative to TMS. The computer spectrum consists of 16 significant transitions. In Figure 1, all lines separated by less than one cycle have simply been added. The result is seen to be a nine-line pattern which is slightly asymmetric owing to slanting. Changing the solvent results in changes in the chemical shifts of H_α, H_β, and H_x, and consequently affects the appearance of the pattern owing to variations in the overlap of the neighboring transitions.

The sample used had more than 90% of the hydroxyl proton exchanged for deuterium by five crystallizations from methanol-O-*d*/D_2O. The necessity for this precaution is apparent from the spectrum of an unexchanged sample in anhydrous pyridine (also shown in Figure 1), where exchange of the hydroxyl proton with solvent is slow (OH appears as a doublet, J = 4.5 cps). In the variable-temperature work (see below), the CHOH pattern of unexchanged samples lost structure in the vicinity of −40°. In the exchanged samples, this complication was avoided.

Consideration of models of **8b** yields an interesting conclusion. The three likely conformers, **9a**–**9c**, all resist efforts to deform them into twist-boat forms. Thus, one may consider as a first approximation only the classical chair forms for the substituted ring (**9a** and **9b**) and the classical boat form (**9c**). Noting that in **9c** the five-spin portion of interest has exactly the same geometrical relations as in a classical chair form where the hydroxyl group is equatorial, we used as models for **9a**–**9c** steroid systems of axial and equatorial alcohols where the A ring is known to be in a pure chair form. The expected coupling constants are then $J_{H_\alpha H_x} \cong$ 10 cps and $J_{H_\beta H_x}$ = 5.5 ± 1.0 cps for the carbinyl proton axial, *i.e.*, **9c**;[13,14] and $J_{H_\alpha H_x} \cong J_{H_\beta H_x}$ = 2.0–3.2 cps for the carbinyl proton equatorial, *i.e.*, **9a** or **9b**.[13]



The most likely deformation from classical forms is a flattening as is found in the parent hydrocarbon. In the boat form, such a deformation would make both dihedral angles between H_x and the vicinal protons smaller than their initial values of 60 and 180°, which would lead to a somewhat smaller value for $J_{H_\alpha H_x}$ and a slightly larger value for $J_{H_\beta H_x}$.[15] For the chair form, flattening would increase one dihedral angle and decrease the other from their initial values of 60°, again with the same qualitative effects on $J_{H_\alpha H_x}$ and $J_{H_\beta H_x}$.[15] The anticipated coupling constants for the boat form, **9c**, are in fair agreement with the values obtained by first-order analysis for the related cases reported in the literature (Table I).

TABLE I
COUPLING CONSTANTS OF CHOH IN BICYCLO[3.3.1]NONANE SYSTEMS BY FIRST-ORDER ANALYSIS

Compd	$J_{H_\alpha H_x}$	$J_{H_\beta H_x}$	Ref
7	11	4	9
8a	10.5	6.0	10
8b	10.5	6.0	11

By double resonance (Table II), the true coupling constants were directly measured.[16] The unusally large separation (*ca.* 1 ppm) between the chemical shifts of H_α and H_β, as indicated by the frequencies of irradiation, is entirely consistent with an additional shielding of the axial protons, H_α, in the chair–boat form by the trimethylene bridge. If the predominant form were the chair–chair, one would expect a normal

(13) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 80 ff.

(14) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1054 (1962).

(15) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(16) For experimental reasons, only one of the coupling constants could be determined for the sample in pyridine solution at room temperature and was found to be 9.8 cps. Thus the unusually clear pattern obtained in pyridine is not the result of any profound change in the conformational mix, *e.g.*, owing to hydrogen bonding.

TABLE II

COUPLING CONSTANTS IN *endo*-BICYCLO[3.3.1]NONAN-3-OL ($CHCl_2CHCl_2$, 60 MHz, TMS = 0)

$J_{H_\alpha H_x}$, cps	$J_{H_\beta H_x}$, cps	Temp, °C	Irradiation frequencies H_α	Irradiation frequencies H_β
10.25 ± 0.25	6.5 ± 0.25	27°	62	127
8.0 ± 0.25	6.0 ± 0.25	117°	72	134

(*ca.* 0.6 ppm) or smaller than normal separation of H_α and H_β.[17] The fact that the unusually shielded proton is the one which is associated with the large constant, as well as the magnitude of the coupling constants, is explicable only on the basis of the chair–boat form, **9c**, which is therefore the predominant conformer. The magnitude of the smaller coupling constant suggests that some flattening of the ring may have occurred.

Raising the temperature affects the larger coupling constant more than the smaller one, as would be expected. Two changes appear in the pattern: (A) the total width decreases from 32.5 cps to 30.0 cps; (B) the deviation of the pattern from a simple septuplet becomes more apparent. These changes in the pattern are consistent with the variation in coupling constants measured by the double-resonance experiments.

It is clear from the data of Table II that the mean coupling constants decrease as the temperature is raised. We interpret this to mean that a *conformational equilibrium is occurring* and that, at higher temperatures, an increasingly important proportion of the mixture has the hydroxyl group axial, either **9a** or **9b**.

As a further proof of the existence of a conformational equilibrium, a variable-temperature study was undertaken and is summarized in Figure 2. The quality of the resolution was verified by measuring the width at half-height of added $CHCl_3$, and this value is listed beneath each pattern. Observation of the expected coalescence at low temperature strongly suggests that there is indeed a conformational equilibrium and that it is rapid at room temperature.

We cannot on the basis of these results identify the minor component. It might be the second boat–chair form, **9b**, the chair–chair form, **9a**, or some mixture of the two. Nor do we have the necessary data to determine the thermodynamic parameters.[18] In particular, we cannot estimate the proportion of the chair–boat form, **9c**, in the equilibrium mixtures other than to say it is clearly by far the major conformer.

The chemical reactivity of **8b** is pertinent here. We have found that treatment of the *endo* alcohol (97.2% isomeric purity) with lead tetraacetate in boiling benzene[19] yields oxaadamantane (89%), the parent ketone (6%), the acetate of the starting alcohol (4%), and an unidentified compound (<1%). Oxidation of the *endo* alcohol by irradiation in the presence of mercuric oxide and iodine leads to essentially pure oxaadamantane in 60% yield.

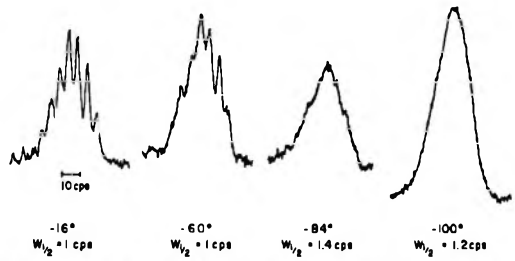


Figure 2.—Spectrum of the carbinyl proton of *endo*-bicyclo[3.3.1]nonan-3-ol at various temperatures; $W_{1/2}$ refers to the width at half-height of added $CHCl_3$.

The *exo* isomer (92% isomeric purity) was found to be rather unreactive to lead tetraacetate, and, when subjected to mercuric oxide oxidation, led to the parent ketone as the major product. A small amount of oxaadamantane was formed from oxidation of the *exo* alcohol, which is easily explained as arising from the *endo* impurity.

From this control reaction, it is clear that there is no epimerization during the oxidation. With respect to the question of conformation, we see that the rate of transannular reaction in the *endo* alcohol, including ring inversion, must be fast with respect to the rate of oxidation to ketone. The rate of a second inversion to the alternate boat–chair form, **9b** (from which it is geometrically impossible to form oxaadamantane), may then be slower or faster than ether formation. In the latter case, one would have a small steady-state concentration of **9a** from which **10** is nonetheless formed in high yield. In either case, the presence of the chair–chair form, **9a**, is required, whereas we presently have no evidence for the alternate boat–chair form, **9b**. Consequently, our personal preference at this time is for the most economical interpretation of the chemical data, *i.e.*, that the chair–chair form, **9a**, is the second contributor to the conformational equilibrium.[20,20a]

Experimental Section[21]

Bicyclo[3.3.1]nonan-3-one was prepared by pyrolysis (350°) of the manganous salt of *cis*-cyclohexane-1,3-diacetic acid. The

(17) The chemical-shift difference of 0.6 ppm or less is the most conservative estimate (*i.e.*, the largest value) taken from the discussion in J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution NMR Spectroscopy," Pergamon Press, Oxford, 1965, p 696 ff. Jackman (L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp 115–119) gives 0.1–0.7 ppm. From examination of the model, one sees that it is difficult to decide whether shielding by the trimethylene bridge will occur in the chair–chair form. If it does, only the equational proton vicinal to the hydroxyl will be affected and δ_{ae} will be less than normal.

(18) For an excellent recent review, see G. Binsch in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Interscience Publishers, New York, N. Y., 1968, p 97.

(19) (a) K. Heusler and J. Kalvoda, *Angew. Chem. Int. Ed. Engl.*, **3**, 525 (1964). (b) Treatment of an *endo*-bicyclo[3.3.1]nonan-3-ol constrained to the chair–chair form is known to yield the bridged ether in high yield: W. A. Ayer, D. A. Law, and K. Piers, *Tetrahedron Lett.*, 2959 (1964).

(20) While this work was in progress, a report appeared [R. A. Appleton, C. Egan, J. M. Evans, S. H. Graham, and J. R. Dixon, *J. Chem. Soc., C*, 1110 (1968)] in which the conformational problem was approached by equilibration of *exo*- and *endo*-3-carbomethoxybicyclo[3.3.1]nonane. The measured value for the greater stability of the *exo* isomer (2.7 kcal/mol) was interpreted on the basis of plausible enthalpy calculations. Without attempting to assess the validity of the assumptions inherent in the work of Graham, *et al.*, it is interesting that the British group conclude that the major conformer is the chair–boat form, analogous to **9c**, the minor conformer is the chair–chair form, and the alternate boat–chair form analogous to **9b** "can certainly be ignored."

(20a) NOTE ADDED IN PROOF.—The isopropoxide-catalyzed equilibration of the epimeric bicyclo[3.3.1]non-3-ols has now been described. A free-energy difference of 2.51 kcal/mol in favor of the *exo* isomer was found [E. N. Marvell and R. S. Knutson, *J. Org. Chem.*, **35**, 388 (1970)], and $\Delta G°$ is thus independent of whether the 3 substituent is hydroxyl or carbomethoxy. If, as suggested, $\Delta G°$ therefore reflects only the skeletal change in the equilibrium the second conformer of **8b** *must* be chair–chair form.

(21) Glpc analyses were performed with an F & M Model 700 instrument using a thermal (W-X filament) detector. Columns used were 10% QF-1 (0.125 in. × 10 ft at 120°) and 10% W-98 (0.125 in. × 6 ft at 120°). By calibration with known mixtures, the relative detector response was found to be as follows (by weight): oxaadamantane, 1.00; bicyclo[3.3.1]nonan-3-one, 1.08; the *exo* alcohol, 1.00; the *endo* alcohol, 1.00; the acetates, 1.22. Combustion analyses were by Spang Microanalytical Laboratories, Ann Arbor, Mich.

yield of bicyclo[3.3.1]nonan-3-one from this procedure was 56–61%.[22]

endo-**Bicyclo[3.3.1]nonan-3-ol (8b).**—To a suspension of lithium aluminum hydride (500 mg) in dry tetrahydrofuran (5 ml), a solution of bicyclo[3.3.1]nonan-3-one (5 g) in tetrahydrofuran (10 ml) was added dropwise and the mixture was then heated at reflux with stirring for 7 hr. After cooling, the excess reagent was decomposed by the addition of water (2 ml) and 5% sodium hydroxide solution (3 ml). The mixture was filtered and the filtrate was concentrated at reduced pressure to give a residue which crystallized on standing. Recrystallization from hexane gave 3.5 g (70%) of **8b**, mp 124–126° (lit.[23] mp 121.5–124°). A second crop (200 mg, 4%), mp 110°, was obtained from the filtrate. Glpc analysis of the derived acetate showed the product to be 97.2% *endo*. The ir and nmr spectra agreed with those reported.[23]

exo-**Bicyclo[3.3.1]nonan-3-ol.**—To a mixture of sodium (4 g, small pieces) in dry benzene (40 ml) was added dropwise a solution of bicyclo[3.3.1]nonan-3-one (1 g) in absolute ethanol (20 ml). The benzene solution was stirred and heated at reflux during the addition (1 hr), after which refluxing was continued for a further 1.5 hr. The solution was cooled and water (25 ml) was added dropwise with stirring. The aqueous phase was separated and extracted twice with 50-ml portions of benzene. The combined benzene extracts were concentrated and the residue was chromatographed on silica gel (3 g). Elution with hexane gave a total of 0.846 g of crude alcohol, uncontaminated with ketone. Recrystallization from hexane followed by sublimation gave 0.469 g (47%), mp 99–100° (lit.[23] mp 100–101°). Glpc analysis of the derived acetate showed the product to be 92.2% *exo*. The infrared and nmr spectra agreed with those reported.[23]

The acetates of the alcohols were prepared from the alcohol by treatment with pyridine–acetic anhydride. The solution was allowed to stand at room temperature for 2 hr and then was heated for 15 min on the steam bath. After cooling, water was added and the product was extracted with chloroform. The chloroform solution was washed successively with 1 *N* hydrochloric acid and water and then dried ($MgSO_4$).

Data for the *exo* acetate follow: ir (CCl_4) 1729, 1239, and 1027 cm^{-1}; nmr (CCl_4 *vs.* TMS) 114.5 (s, 3 H) and 309–339 cps (m, 1 H).

Data for the *endo* acetate follow: ir (CCl_4) 1727, 1741, 1229, 1250, 1022, and 1044 cm^{-1}; nmr (CCl_4 *vs.* TMS) 117 (s, 3 H) and 287–310 cps (br, 1 H).

A mixture of the acetates was purified by preparative glpc and analyzed.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.48; H, 9.95. Found: C, 72.69; H, 9.84.

(22) We thank Dr. John Schaefer for the details of this improved procedure.

(23) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

Lead Tetraacetate Reactions.[24]—A mixture of dry benzene (10 ml), commercial lead tetraacetate (2.0 g), and calcium carbonate (1.0 g) was heated for 15 min at reflux in a flask fitted with condenser and drying tube. The alcohol (300 mg in 10 ml of benzene) was then added in one batch through the condenser and refluxing was continued for 3 hr. The mixture was cooled and water (5 ml) was added with stirring during 30 min. After filtration, the solution was concentrated by distillation through a short Vigreux column and the residue was sublimed at 140° (1 atm).

From *endo*-bicyclo[3.3.1]nonan-3-ol there was obtained 255 mg (86%) of oxaadamantane (purity 89%) contaminated with ketone (6%), *endo* acetate (4%), and an unidentified compound (<1%). From *exo*-bicyclo[3.3.1]nonan-3-ol there was obtained 221 mg (74%) of unreacted alcohol together with trace amounts of the ketone and acetate.

Mercuric Oxide–Iodine Reactions.[24]—Iodine (4.0 g) and mercuric oxide (4.0 g) were placed in a 100-ml pear-shaped flask fitted with a side arm. The alcohol (300 mg) in carbon tetrachloride (75 ml) was added, and a condenser was attached. Agitation of the mercuric oxide suspension was maintained by bubbling in nitrogen through the side arm during irradiation with a GE 275-W sun lamp for 3.5 hr. Inorganic material was removed by filtration and the filtrate was concentratd by distillation through a short Vigreux column.

From *endo*-bicyclo[3.3.1]nonan-3-ol there was obtained 178 mg (60%) of essentially pure oxaadamantane.

From *exo*-bicyclo[3.3.1]nona-3-ol there was obtained 141 mg (47%) of a mixture containing the ketone and two unidentified compounds.

Oxaadamantane.—A sample was purified by chromatography on silica gel: mp 225–230° (sealed tube) (lit.[25] mp 232°); ir (CCl_4) 1020 and 1090 cm^{-1}; nmr (CCl_4 *vs.* TMS) 3.73–4.03 (2 H) and 1.4–2.25 ppm (12 H).

Nmr spectra were recorded either on a Varian Associates A-56-60A spectrometer or on an HA-60 (variable-temperature and decoupling measurements) at *ca.* 60-MHz operating frequency. High temperatures were calibrated by chemical shifts of ethylene glycol; low temperatures were calibrated with an iron-constantan thermocouple.

Registry No.—**8b**, 10036-10-9; **10**, 281-24-3; *exo*-bicyclo[3.3.1]nonan-3-ol, 10036-08-5; *exo*-bicyclo[3.3.1]-nonan-3-ol acetate, 23825-38-9; *endo*-bicyclo[3.3.1]-nonan-3-ol acetate 19490-34-7.

Acknowledgment.—This work was supported by Grant 1022-01 from the Petroleum Research Fund, which we acknowledge with pleasure.

(24) Yields are corrected for epimeric impurities in each starting material.

(25) H. Stetter and P. Tacke, *Chem. Ber.*, **96**, 694 (1963).

Bridgehead Substitution *vs.* Ring Contraction in the Deamination of 1-Aminobicyclo[2.2.1]hept-5-en-2-ol

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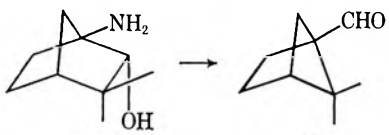
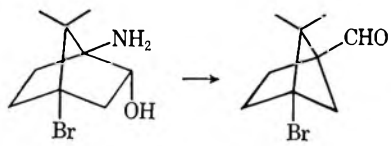
Received October 31, 1969

The synthesis of *endo*-1-aminobicyclo[2.2.1]hept-5-en-2-ol (**13**) is described. Deamination reactions resulted in bridgehead substitution rather than the ring contraction characteristic of the corresponding saturated amines. This result can be rationalized on the basis of the increase in steric strain which would be encountered in the rearrangement process, but not in the competing substitution.

The deamination of vicinal aliphatic amino alcohols provides many examples of molecular rearrangement.[2] Recently, Larson and coworkers[3] observed that the nitrous acid deamination of amino alcohols **1** and **2** led, *via* semipinacolic rearrangement, to the aldehydes **3** and **4** as the sole isolable products in *ca.* 70% yield.



1 **3**



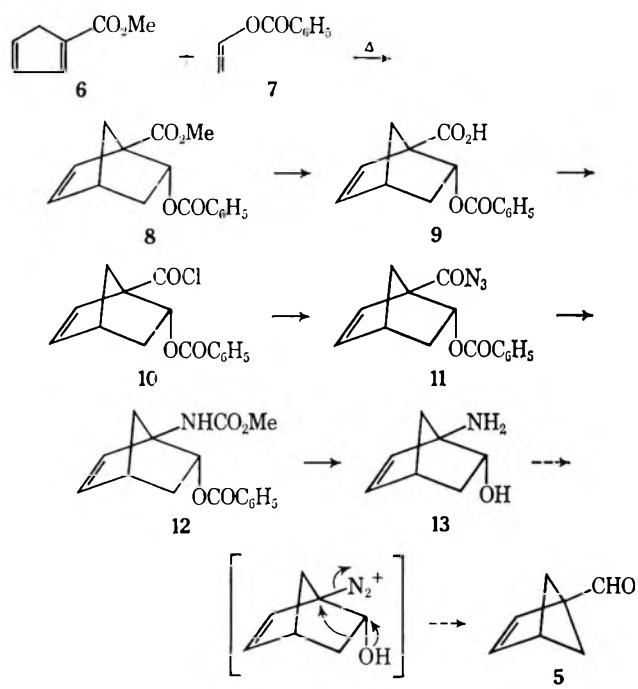
2 **4**

This observation is compatible with the proposal of Pollak and Curtin[4] that the nature of the rearranged product in these reactions is dependent on the *trans*-coplanar relationship between the migrating group and the departing nitrogen. The present investigation describes an attempt to prepare a bridgehead-substituted bicyclo[2.1.1]hex-2-ene (**5**) based on this type of rearrangement. Toward this end, a desirable compound for study appeared to be 1-aminobicyclo[2.2.1]-hept-5-en-2-ol (**13**), the synthesis of which is outlined in Chart I.

The initial step involved the Diels–Alder reaction between "Thiele's ester" **6** and vinyl benzoate **7**. The desired diester **8** could be isolated in 14% yield from the resultant mixture of adducts. Selective cleavage of the methyl ester of **8** with anhydrous lithium iodide in refluxing pyridine[5] gave the acid benzoate **9** in 92% yield. The Curtius reaction[6] provided an efficient method of degrading this bridgehead carboxylic acid to the corresponding carbamate **12**, obtained as a white, crystalline solid in 81% overall yield from **9** after recrystallization from hexane–ether.

The nuclear magnetic resonance (nmr) spectrum of **12** provides strong support for its assigned structure and

CHART I



stereochemistry. It shows a one-proton pair of doublets (J_1 = 8 cps, J_2 = 3 cps) centered at τ 4.4, assigned to the proton on the carbon bearing an oxygen, a broad one-proton singlet at τ 7.26 (H-4), and a one-proton septet at τ 7.65 (*exo* H-3), along with other characteristic absorption signals. Proof that the carbamate group is adjacent to the benzoate group was obtained in conducting double-resonance experiments. If the benzoate group is in fact located at the C-2 position, irradiation at the H-4 should have no effect on the τ 4.4 splitting pattern. This is indeed the case. The τ 4.4 (H-2) absorption remains a pair of doublets, while the τ 7.65 (*exo* H-3) absorption collapses to an overlapping pair of doublets (J_3 = 8 cps, J_4 = 12 cps). That the benzoate group was *endo* was verified by the absence of long-range *anti*-H-7–*endo*-H-2 coupling.[7] Basic hydrolysis of **12** gave the desired amino alcohol **13** in 96% yield.

When the nitrous acid deamination of **13** was carried out under conditions reported to give maximum rearrangement,[2a,3] a mixture containing two major com-

(1) National Institutes of Health Predoctoral Fellow, 1966–1969.

(2) (a) M. Cherest, H. Felkin, J. Sicher, F. Sipos, and M. Tichy, *J. Chem. Soc.*, 2513 (1965); (b) G. E. McCasland, *J. Amer. Chem. Soc.*, **73**, 2293 (1951); (c) J. W. Huffman and J. E. Engle, *J. Org. Chem.*, **24**, 1844 (1959); (d) J. G. Traynham and M. T. Yang, *J. Amer. Chem. Soc.*, **87**, 2394 (1965).

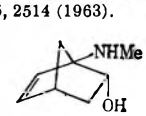
(3) (a) K. Ebisu, L. B. Batty, J. M. Higaki, and H. O. Larson, *ibid.*, **88**, 1995 (1966); (b) H. O. Larson, T. Ooi, W. Luke, and K. Ebisu, *J. Org. Chem.*, **34**, 525 (1969).

(4) P. I. Pollak and D. Y. Curtin, *J. Amer. Chem. Soc.*, **72**, 961 (1950).

(5) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).

(6) P. A. S. Smith, *Org. React.*, **3**, Chapter 9 (1946).

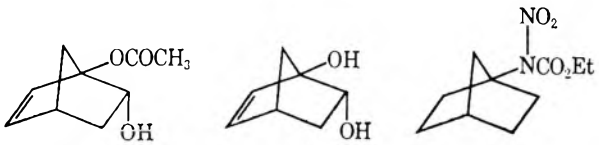
(7) Compounds **12** and **14** show long-range *endo*-H-3–*anti*-H-7 coupling constants of 4.0 and 3.5 cps, respectively; *cf.* J. Meinwald and Y. C. Meinwald, *J. Amer. Chem. Soc.*, **85**, 2514 (1963).



14

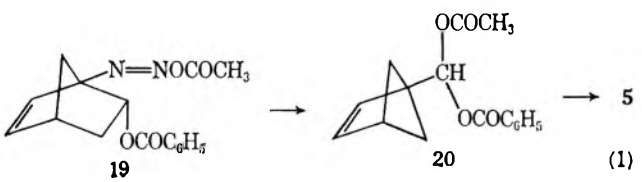
ponents could be isolated in good yield. Neither proved to be the desired ring-contracted aldehyde. The mixture was separated by preparative tlc, and the faster moving component (*ca.* 27% of mixture) was assigned structure **15** on the basis of its infrared and nmr spectra. Vacuum sublimation of the second major component (*ca.* 66% of mixture) gave a crystalline diol, assigned structure **16**, the nmr spectrum of which exhibited the same characteristic bicyclo[2.2.1]hept-5-ene absorption as **15**, as well as a two-proton singlet at τ 7.0 exchangeable with deuterium oxide. The mass spectrum of **16** shows an intense *m/e* 82 peak which is compatible with fragmentation *via* a retro Diels–Alder reaction.[8,9]

When it became apparent that unrearranged bridgehead substitution products were being formed in preference to ring contraction, an alternative deamination technique was sought. Recently, White and coworkers[10] have observed the formation of a relatively



15 16 17

large percentage of solvent-derived products in the thermal decomposition of the N-nitrourethan **17**, derived from 1-norbornylamine, in nonpolar solvents. In their explanation of these results, the authors concluded that a large fraction of relatively "free" carbonium ions were being formed. If this were correct, a hydroxyl group at the 2 position might be expected to facilitate ring contraction during decomposition. With this in mind, a study of the thermolysis of N-nitroso-1-acetamidobicyclo[2.2.1]hept-5-en-2-yl benzoate (**18**) wasun dertaken, with the hope that the intermediate diazo ester **19** would undergo rearrangement upon dissociation to give the diester **20**, which on hydrolysis would give the desired aldehyde **5** (eq 1).



19 20 (1)

In fact, thermal decomposition of a carbon tetrachloride solution of **18**, prepared as shown in Chart II, led to formation of a product shown to be a mixture of the bridgehead acetate **21** (*ca.* 28%) and bromide **22** (*ca.* 42%).[11] In addition, 26% of the amide benzoate **23** could be recovered. No trace of the desired rearrangement product was observed in the nmr spectrum of the crude reaction mixture. The structures **21** and **22** were assigned on the basis of the similarity of their nmr and mass spectra to those of other bicyclo[2.2.1]hept-5-enes encountered in this work. In each case a major

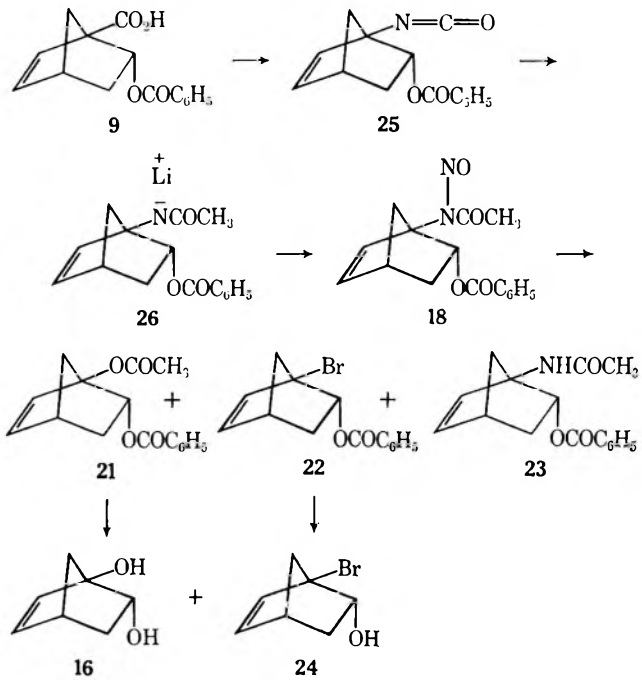
(8) T. Goto, A. Tatamatsu, Y. Hata, R. Muneyuki, H. Tanida, and K. Tori, *Tetrahedron*, **22**, 2213 (1966).

(9) S. J. Cristol, R. A. Sanchez, and T. C. Morrill, *J. Org. Chem.*, **31**, 2738 (1966).

(10) E. H. White, H. P. Tiwari, and M. J. Todd, *J. Amer. Chem. Soc.*, **90**, 4734 (1968).

(11) The bromide ion was presumably supplied by the lithium bromide present in the methyllithium used in the synthesis of the nitroso amide.

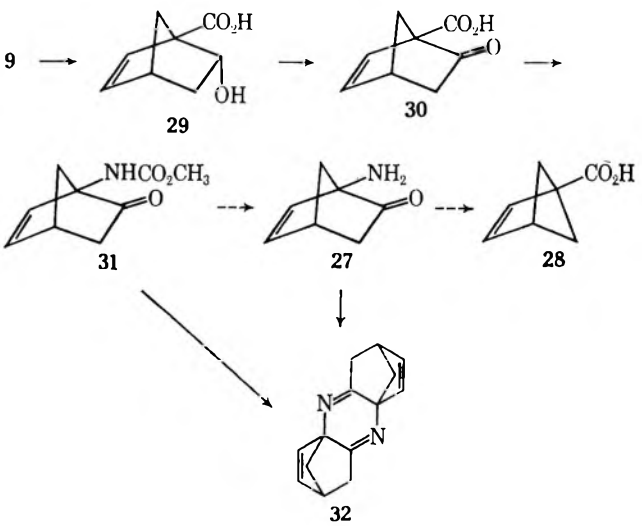
CHART II



fragment ion in the mass spectrum was the result of a retro Diels–Alder reaction. Supporting spectral evidence was obtained from the corresponding alcohols **16** and **24**. Apparently, if any "free" carbonium ions were formed in the thermolysis of **18**, bridgehead substitution to give unrearranged product was energetically more favorable than the desired ring contraction.

During the course of this investigation an attempt was made to prepare the amino ketone **27**, as summarized in Chart III, with the hope that nitrous acid deam-

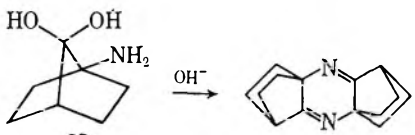
CHART III



ination of **27** might lead, *via* the appropriate rearrangement, to the bridgehead carboxylic acid **28**. Unfortunately, basic hydrolysis of the carbamate **31** led to the dihydropyrazine **32** rather than the expected amino ketone. The assignment of structure **32** is based on its characteristic infrared, nmr, and mass spectra, and finds analogy in a report by Applequist[12]

(12) D. E. Applequist and J. P. Klieman, *J. Org. Chem.*, **26**, 2178 (1961).

of the formation of a similar dihydropyrazine **34** on treatment of **33** with aqueous sodium hydroxide.



33 34

In rationalizing the failure of **13** to undergo the desired semipinacolic ring contraction,[13] we conclude that the 5,6 double bond raises the transition-state energy associated with ring contraction such that ion-pair collapse to solvent-derived products is favored. This is not unreasonable, since bridgehead substitution does not change the environment of the double bond, while rearrangement would force the double bond into a more strained ring system. This steric factor apparently renders Larson's elegant synthesis of bicyclo[2.1.1]hexanes inapplicable to the corresponding olefins.

Experimental Section

Diels–Alder Reaction between Vinyl Benzoate and Thiele's Ester. 1-Carbomethoxybicyclo[2.2.1]hept-5-en-2-yl Benzoate (8).[14]—A mixture of 112 g (0.758 mol) of freshly distilled vinyl benzoate, 28.2 g (0.228 mol) of freshly distilled Thiele's ester, bp 87–90° (16 mm), and 400 mg of hydroquinone was heated at 180° under nitrogen for 48 hr. Fractional distillation gave 57.1 g (92%) of a mixture of adducts, bp 144–154° (0.5 mm). This mixture was dissolved in 120 ml (2.7 mol) of dimethylamine and stored at 0° for 18 hr. The excess amine was removed with little or no heating. The residue was dissolved in ether, and the ether was extracted with 250 ml of 1.0 *N* HCl, washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to give 25 g (44%) of an oil. Vacuum distillation gave 21.7 g of a mixture, bp 144–154° (0.5 mm), which showed two methoxyl peaks at τ 6.25 and 6.3 in the nmr. Silica gel column chromatography gave 7.4 g of a mixture highly enriched in the desired adduct **8**: ir ($CHCl_3$) 1728 (COOMe), 1603, 1440, 1310, 1280–1180, and 1110 cm^{-1}; nmr (CCl_4) τ 2.0 (m, 2) and 2.6 (m, 3, aromatic), 3.62 (m, 2, olefinic), 4.17 (q, 1, J_1 = 8 cps, J_2 = 3 cps, H-2), 6.25 (s, 3, COOMe), 7.0 (s, 1, H-4), 7.48 (septet, 1, *exo* H-3), 8.12 (m, 2, *syn* and *anti* H-7), and 8.8 (m, 1, *endo* H-7).

1-Carboxybicyclo[2.2.1]hept-5-en-2-yl Benzoate (9).—A solution of 56.5 g (421 mmol) of anhydrous lithium iodide and 11.4 g (42.1 mmol) of **8** in 1200 ml of anhydrous pyridine was refluxed under nitrogen for 3 days, poured over crushed ice, neutralized (concentrated HCl) with external cooling, and extracted with ether. The ether extract was concentrated under reduced pressure and extracted with 40 ml of 1 *N* NaOH solution. Ether extraction of the reacidified solution gave 9.9 g (91%) of product, which when recrystallized from hexane–ether gave 5.36 g (49%) of crystalline acid benzoate **9**: mp 138–141°; ir ($CHCl_3$) 3500–2500, 1715, 1605, 1588, 1450, 1315, 1275–1195, and 1110 cm^{-1}; nmr ($CDCl_3$) τ −2.0 (s, 1, COOH), 1.6–2.74 (m, 5, aromatic), 3.23–3.60 (m, 2, H-5, H-6), 3.95 (q, 1, J_1 = 8 cps, J_2 = 3 cps, H-2), 6.8 (s, 1, H-4), 7.29 (septet, 1, *exo* H-3), 8.0 (m, 2, *syn* and *anti* H-7) and 8.5 (m, 1, *endo* H-3).

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.42. Found: C, 69.60; H, 5.41.

N-Carbomethoxy-1-aminobicyclo[2.2.1]hept-5-en-2-yl Benzoate (12).—A 2.9-g (11.2 mmol) sample of **9** was dissolved in 23 ml of 0.5 *N* NaOH and evaporated under reduced pressure (30°). The residue was dried overnight at 100° in a vacuum oven, suspended in 100 ml of anhydrous benzene, and cooled to 0°. To the vigorously stirred suspension was added 5 drops of pyridine and 4.27 g (34 mmol) of oxalyl chloride. After 15 min at 0° and 30 min at room temperature excess oxalyl chloride and solvent were removed under reduced pressure and the residue was dissolved in anhydrous benzene, filtered, and evaporated to give **10**, which had infrared (neat) absorption at 1790, 1723, 1605, 1585, 1452, 1272, 1111, 790, 740, and 700 cm^{-1}. A solution of 2.21 g (34 mmol) of sodium azide in 5.5 ml of water was added with stirring under nitrogen to a chilled solution of **10** in 125 ml of acetone. After 30 min at 0° an equal volume of water was added and the solution was extracted with ether. Evaporation of the dried ($MgSO_4$) extract gave **11**, which showed infrared ($CHCl_3$) absorption at 2139, 1712, 1603, 1585, 1450, 1310 (d), 1275, 1160, 1113, 968, and 950 cm^{-1}. The azide was refluxed in equal volumes of anhydrous methanol and benzene (20 ml) for 12 hr under nitrogen. Evaporation of solvent gave **12**, which on recrystallization from hexane–ether gave 2.59 g (81%) of white needles: mp 131–133°; ir ($CHCl_3$) 3440, 1723, 1604, 1588, 1500, 1450, 1342, 1270–1180, and 1110 cm^{-1}; nmr ($CDCl_3$) τ 2.0–2.9 (m, 5, aromatic), 3.75 (q, 1, J_1 = 6 cps, J_2 = 4 cps, H-5), 3.87 (s, 1, NH), 3.98 (br d, 1, J_1 = 6 cps), 4.4 (qt, 1, J_3 = 8 cps, J_4 = 3 cps, H-2), 6.47 (s, 3, COOMe), 7.26 (m, 1, H-4), 7.65 (septet, 1, *exo* H-3), 7.95 (m, 1, *syn* H-7), 8.3 (d, 1, J_5 = 8.5 cps, *anti* H-7), and 8.8 (pair of overlapping doublets, 1, J_6 = 12 cps, *endo* H-3). Double irradiation at 277.4 cps downfield from TMS caused the following changes: H-5 absorption collapsed to a doublet (J_1 = 6 cps), *exo* H-3 collapsed to overlapping pair of doublets (J_3 = 8 cps, J_6 = 12 cps), and the *syn* H-7 collapsed to a doublet of doublets (J_5 = 8.5 cps, J_7 = 4 cps).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.90; H, 5.97; N, 4.88. Found: C, 66.96; H, 5.99; N, 5.02.

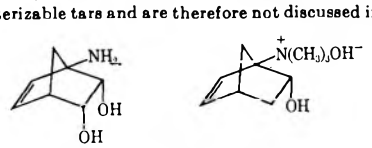
1-Aminobicyclo[2.2.1]hept-5-en-2-ol (13).—A suspension of 958 mg (3.33 mmol) of **12** in a tenfold excess of alcoholic aqueous potassium hydroxide was refluxed under nitrogen for 40 hr. The methanol was removed under vacuum and the residual aqueous solution was continuously extracted with ether to give 400 mg (96%) of **13**: ir ($CHCl_3$) 3570–3080, 3370, 1650, 1580, 1460, 1400, 1350, 1260, 1110, 1080, 1050, and 990 cm^{-1}; nmr ($CDCl_3$) τ 3.67 (q, 1, J_1 = 5.5 cps, J_2 = 3.4 cps, H-5), 4.2 (d, 1, J_1 = 5.5 cps, H-6), 5.93 (q, 1, J_3 = 8 cps, J_4 = 3 cps, H-2), 7.36 (m, 1, H-4), 7.53 (s, 3, NH_2, OH), 7.78 (septet, 1, *exo* H-3), 8.64 (m, 2, *syn* and *anti* H-7), and 9.07 (m, 1, *endo* H-3).

Deamination of 1-Aminobicyclo[2.2.1]hept-5-en-2-ol (13).—To an ice-cold solution of 351 mg (2.81 mmol) of amine **13** in 12 ml of 50% acetic acid was added 776 mg (11.2 mmol) of sodium nitrite in 4 ml of water. The solution was stirred for 1 hr at 0° and 1 hr at room temperature, neutralized (Na_2CO_3), and continuously extracted with ether to give 265 mg of product: ir ($CHCl_3$) 3580, 3420, 1723, 1650, 1540, 1375, 1350, 1270, 1180, 1160, 1000, and 905 cm^{-1}; nmr ($CDCl_3$) τ −0.4 (s), −0.1 (s), 3.55–4.16 (m, 2, olefinic), 5.67 (m, 1, H-2), 5.95 (s, *ca.* 2.3), 7.0 (m, *ca.* 0.43), 7.36 (m, 1, H-4), 7.88 (s, *ca.* 0.86, COOMe), 7.73 (m, 2), 8.21 (m, 1), 8.47 (m, 2), and 8.93 (m, 2). Preparative thin layer chromatography of 150 mg of this product gave 41 mg of **15** (contaminated with some **16**): ir ($CHCl_3$) 3580, 3400, 1723, 1375, and 1270 cm^{-1}; nmr ($CDCl_3$) τ 3.63 (q, 1, J_1 = 6 cps, J_2 = 3 cps, H-5), 3.83 (d, 1, J_1 = 6 cps, H-6), 5.58 (q, 1, J_3 = 8 cps, J_4 = 2.5 cps, H-2), 6.53 (s, 1, OH), 7.25 (m, 1, H-4), 7.87 (s, 3, COOMe), 7.71 (septet, 1, *exo* H-3), and 8.0–9.2 (m, 3, *syn* and *anti* H-7, *endo* H-3). Vacuum sublimation at 100° (0.5 mm) of the second fraction gave 46 mg of crystalline diol **16**: mp 173–175° dec (sealed tube); ir ($CHCl_3$) 3580, 3400, 1605, 1580, 1460, 1400, 1350, 1160, 1085, 1040, 990, and 910 cm^{-1}; nmr ($CDCl_3$) τ 3.65 (q, 1, J_1 = 5.8 cps, J_2 = 3.2 cps, H-5), 4.11 (d, 1, J_1 = 5.8 cps, H-6), 5.86 (q, 1, J_3 = 8 cps, J_4 = 3 cps, H-2), 7.0 (s, 2, OH), 7.3 (m, 1, H-4), 7.73 (septet, 1, *exo* H-3), 8.57 (m, 2, *syn* and *anti* H-7), and 8.97 (m, 1, *endo* H-3); mass spectrum (70 eV) *m/e* (rel intensity) 107 (0.4), 105 (0.4), 95 (1), 83 (8), 82 (100), 81 (9), 79 (2), 77 (3), 67 (0.9), 65 (1), 63 (0.9), 54 (5), 53 (9), 52 (2), and 51 (3).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.67; H, 7.94. Found: C, 66.87; H, 8.17.

Thermal Decomposition of N-Nitroso-1-acetamidobicyclo[2.2.1]hept-5-en-2-yl Benzoate (18).—A benzene solution of acid azide **11**, obtained from 1.5 g of **9**, was refluxed under nitrogen for 36 hr to give 1.5 g of isocyanate **25**: ir (CCl_4) 2260, 1730, 1605, 1580, 1455, 1270, and 1110 cm^{-1}. An ether solution

(13) During the course of this study the aminodiol **35** and the quaternary salt **36** were also synthesized. Subsequent reactions of these compounds led to uncharacterizable tars and are therefore not discussed in detail.



35 36

(14) D. Peters, *J. Chem. Soc.*, 1042 (1961).

of **25** was added to a 100-ml, three-neck flask, the flask was flushed with nitrogen and cooled to −78°, and 2.9 ml (5.8 mmol) of 2 *M* ethereal methyllithium solution was added with vigorous stirring. After 2 hr at −78° the solution was gradually warmed to room temperature, the ether was evaporated under a stream of nitrogen, and 25 ml of CCl_4 was added. The solution was cooled to −50° and then 1.43 g (17.5 mmol) of fused sodium acetate and 7 ml of a 0.0185 *M* solution of N_2O_4 in CCl_4 were added with stirring. The solution was slowly warmed to room temperature and then heated at 70° for 16 hr. The suspended solid was filtered and the filtrate was evaporated to give 1.12 g of product. Ether extraction of an aqueous solution of the filtered solid gave 435 mg of amide **23** (26%). Preparative tlc followed by sublimation at 110° (0.5 mm) gave a white, crystalline solid: mp 156–158°; ir ($CHCl_3$) 3390, 3060, 1715, 1675, 1588, 1502, 1455, 1345, 1280, and 1115 cm^{-1}; nmr ($CDCl_3$) τ 1.85–2.6 (m, 5, aromatic), 3.08 (br, 1, NH), 3.6 (q, 1, J_1 = 6 cps, J_2 = 3.5 cps, H-5), 3.9 (d, 1, J_1 = 6 cps, H-6), 4.25 (q, 1, J_3 = 8 cps, J_4 = 2.5 cps, H-2), 7.1 (m, 1, H-4), 7.5 (m, 2, *exo* H-3, *syn* H-7), 8.0 (s, 3, COMe), 8.28 (d, 1, J_5 = 8 cps, *anti* H-7) and 8.7 (m, 1, *endo* H-3); mass spectrum (70 eV) *m/e* (rel intensity) 167 (2.5), 166 (17.3), 149 (3.1), 124 (37.8), 123 (100), 107 (5.3), 105 (33.3), 81 (66.7), 80 (12.6), 77 (22.8), 66 (1.0), 65 (1.5), 53 (3.6), 51 (6.4), and 43 (17.3), metastable peaks at *m/e* 79.5 (149–107), 56.5 (105–77), 53.4 (123–81), 51.5, 35.2 (81–53), and 33.8 (77–51).

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.85; H, 6.27; N, 5.17. Found: C, 71.17; H, 6.42; N, 4.94.

Two major components could be isolated from the 1.12 g of product by repeated Florisil column chromatography. Vacuum sublimation at 60° (0.5 mm) of the faster moving component (*ca.* 57% of mixture) gave a white, crystalline solid, **22**: mp 74–75°; ir (CCl_4) 3060, 1730, 1605, 1585, 1455, 1330, 1315, 1285, 1275, 1115, and 1105 cm^{-1}; nmr (CCl_4) τ 1.9–2.9 (m, 5, aromatic), 3.75 (m, 2, olefinic), 4.5 (q, 1, J_1 = 8 cps, J_2 = 3 cps, H-2), 7.15 (m, 1, H-4), 7.5 (m, 1, *exo* H-3), 8.0 (m, 2, *syn* and *anti* H-7), and 8.67 (m, 1, *endo* H-3); mass spectrum (70 eV) *m/e* (rel intensity) 294 (3.0), 292 (3.0), 248 (0.4), 213 (0.2), 189 (0.3), 187 (0.3), 149 (4.5), 146 (7.7), 106 (7.7), 105 (100), 77 (28.6), 65 (6.5), and 51 (8.3), metastable peaks at *m/e* 56.5 (105–77) and 29.1 (144/146–65). Basic hydrolysis of **22** gave, after preparative tlc, 12 mg of **24**: ir (CCl_4) 3590, 3460, 3138, 3060, 1338, 1305, 1275, 1235, 1130, 1110, 1070, 1040, 995, 975, and 875 cm^{-1}; nmr ($CDCl_3$) τ 3.38 (q, 1, J_1 = 6 cps, J_2 = 3 cps, H-5), 3.67 (d, 1, J_1 = 6 cps, H-6), 5.26 (q, 1, J_3 = 8 cps, J_4 = 3 cps, H-2), 6.8 (s, 1, OH), 7.0 (m, 1, H-4), 7.48 (septet, 1, *exo* H-3), 7.86 (m, 2, *syn* and *anti* H-7), and 8.67 (m, 1, *endo* H-3); mass spectrum (70 eV) *m/e* (rel intensity) 146 (100), 144 (100), 125 (9), 123 (11), 111 (15), 97 (24), 83 (22), 81 (27), 65 (83), and 55 (40). Preparative tlc of the second major component (*ca.* 38% of mixture) gave essentially pure **21**: ir (CCl_4) 3060, 1755, 1730, 1655, 1605, 1585, 1455, 1370, 1340, 1315, 1275, 1235, 1175, and 1110 cm^{-1}; nmr (CCl_4) τ 2.0–2.9 (m, 5, aromatic), 3.78 (m, 2, olefinic), 4.2 (q, 1, J_1 = 8 cps, J_2 = 3 cps, H-2), 7.2 (m, 1, H-4), 7.53 (m, 1, *exo* H-3), 7.98 (m, 2, *syn* and *anti* H-7), 8.0 (s, 3, COOMe), and 8.7 (m, 1, *endo* H-3); mass spectrum (70 eV) *m/e* (rel intensity) 272 (0.2), 258 (0.2), 230 (0.7), 168 (1.0), 167 (8), 149 (1.0), 126 (4), 125 (44), 124 (44), 107 (4), 106 (8), 105 (100), 82 (59), 81 (7), 77 (52), 67 (4), 65 (3), and 43 (48). Basic hydrolysis of **21** followed by vacuum sublimation of the product at 100° (0.5 mm) gave 20 mg of diol **16**.

1-Carboxybicyclo[2.2.1]hept-5-en-2-ol (29).—A solution of 3.91 g (15.2 mmol) of **9** in 60.8 ml of 0.5 *N* sodium hydroxide was stirred at room temperature under nitrogen for 12 hr. The solution was acidified (1.0 *N* HCl) and extracted with ether, and the ether was dried ($MgSO_4$) and evaporated to give 4.19 g of a mixture of benzoic acid and **29**. This mixture was digested in 75 ml of hexane and cooled, and the suspended solid was filtered to give, after recrystallization from acetone, 1.45 g (62%) of crystalline **29**: mp 162–164° dec; ir (KBr) 3600–2500, 3320, 1700, 1340, 1313, 1270, 1258, 1068, 1055, 930, 820, and 705 cm^{-1}; nmr (CD_3COCD_3) τ 3.6 (q, 1, J_1 = 6 cps, J_2 = 3 cps, H-5), 3.84 (d, 1, J_1 = 6 cps, J_2 = 3 cps, H-5), 3.84 (d, 1, J_1 = 6 cps, H-6), 1.8–4.63 (br, 2, COOH, OH), 5.2 (q, 1, J_3 = 8 cps, J_4 = 3 cps, H-2), 7.15 (m, 1, H-4), 7.73 (septet, 1, *exo* H-3), 8.37 (m, 2, *syn* and *anti* H-7), and 9.0 (m, 1, *endo* H-3).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.34; H, 6.49. Found: C, 62.58; H, 6.69.

1-Carboxybicyclo[2.2.1]hept-5-en-2-one (30).—A solution of 700 mg (4.53 mmol) of **29** in 5 ml of anhydrous pyridine was added to a stirred solution of 7 g (27.2 mmol) of Collins reagent[15] in 95 ml of pyridine. After 12 hr at room temperature the suspension was poured over ice, neutralized (concentrated HCl) with external cooling, and extracted repeatedly with ether. The ether was dried ($MgSO_4$) and evaporated and the residue was vacuum sublimed twice at 70° (0.5 mm) to give 457 mg (66%) of crystalline **30**: mp 119–121°; ir ($CHCl_3$) 3600–2500, 1790 (sh), 1770, 1760, 1720, 1310, 1100, 990, and 970 cm^{-1}; nmr ($CDCl_3$) τ −1.5 (s, 1, COOH), 3.3 (q, 1, J_1 = 6 cps, J_2 = 3 cps, H-5), 3.6 (d, 1, J_1 = 6 cps, H-6), 6.74 (m, 1, H-4), and 7.55–7.87 (m, 4, *syn* and *anti* H-7, *exo* and *endo* H-3); mass spectrum (70 eV) *m/e* (rel intensity) 153 (2.3), 152 (2.5), 135 (0.4), 124 (8.4), 110 (100), 105 (1.2), 93 (9.6), 82 (55.8), 79 (15.4), 77 (15.4), 66 (82.8), 65 (21.2), 51 (11.5), and 45 (6), metastable peaks at *m/e* 101.5, 64.5 (135–93), 61.5 (110–82), and 39.6 (110–66).

Anal. Calcd for $C_8H_8O_3$: C, 63.16; H, 5.26. Found: C, 63.13; H, 5.10.

Attempted Preparation of 1-Aminobicyclo[2.2.1]hept-5-en-2-one (27).—A suspension of the sodium salt of the keto acid **30**, when treated with 1 equiv of oxalyl chloride as described above, gave an acid chloride: ir (CCl_4) 1818, 1789, 1757, 1480, 1232, 1175, 1085, 1036, and 870 cm^{-1}. The acid chloride was dissolved in acetone, cooled to 0°, and treated with 1 equiv of sodium azide to give an acid azide: ir 2130, 1770, 1715, 1298, 1256, 1175, and 945 cm^{-1}. The crude carbamate obtained by methanolysis of the azide was chromatographed through Florisil to give 307 mg (49%) of crystalline keto carbamate **31**: mp 80–81°; ir ($CHCl_3$) 3403, 1755, 1731, 1605, 1580, 1504, 1455, 1260, 1085, and 1000 cm^{-1}; nmr ($CDCl_3$) 3.45 (q, 1, J_1 = 5.5 cps, J_2 = 3.2 cps, H-5), 4.0 (q, 1, J_1 = 5.5 cps, J_3 = 1 cps, H-6), 4.18 (s, 1, NH), 6.33 (s, 3, COOMe), 6.86 (m, 1, H-4), 7.1 (m, 1, *exo* H-3), and 7.92 (m, 3, *syn* and *anti* H-7, *endo* H-3); mass spectrum (70 eV) *m/e* (rel intensity) 181 (0.3), 153 (100), 150 (2.4), 139 (29.2), 121 (12.1), 120 (19.1), 108 (5), 107 (32.1), 94 (23.1), 80 (13.6), 79 (12.1), 78 (29.2), 67 (15.5), 66 (8.5), 65 (5.6), 59 (14.6), and 53 (19.1), metastable peaks at *m/e* 104.3, 94.8 (153–120), 82.7 (139–107), and 39.8 (107–65).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.76; H, 6.08; N, 7.73. Found: C, 60.05; H, 6.17; N, 7.84.

A solution of 265 mg (1.46 mmol) of **31** and 818 mg (14.6 mmol) of potassium hydroxide in equal volumes of methanol and water (5 ml) was refluxed for 12 hr under nitrogen. The methanol was evaporated and the residue was continuously extracted with ether to give 112 mg of **32** (73%). Vacuum sublimation at 80° (0.5 mm) gave 70 mg of a waxy solid: ir (CCl_4) 3060, 1678, 1430, 1328, 1240, 1125, 1105, 1045, and 900 cm^{-1}; nmr (CCl_4) 3.66 (q, 2, J_1 = 5.5 cps, J_2 = 3 cps, H-5, H-5′), 4.36 (d, 2, J_1 = 5.5 cps, H-6, H-6′), 7.01 (m, 2, H-4, H-4′), and 7.43–9.26 (m, 8); mass spectrum (70 eV) *m/e* (rel intensity) 210 (27), 209 (27), 195 (14), 183 (3.6), 168 (6.7), 145 (6.1), 132 (18), 105 (100), 91 (14), 78 (12), 77 (14), and 65 (60); high resolution (measured *m/e*, elemental composition, calculated mass) 210.1160, $C_{14}H_{14}N_2$, 210.1160; 145.0765, $C_9H_9N_2$, 145.0766; 105.0578, C_7H_7N, 105.0578; 91.0547, C_7H_7, 91.0545; 78.0469, C_6H_6, 78.0462; and 65.0391, C_5H_5, 65.0383.

Registry No.—**8**, 23939-72-2; **9**, 23972-87-4; **12**, 23939-73-3; **13**, 23939-74-4; **15**, 23972-88-5; **16**, 23939-75-5; **21**, 23972-89-6; **22**, 23939-76-6; **23**, 23939-77-7; **24**, 23939-78-8; **29**, 23939-79-9; **30**, 23936-82-5; **31**, 23936-83-6; **32**, 23936-84-7.

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Desulfonylation of Aromatic Sulfonyl Halides Catalyzed by Some Platinum–Metal Complexes

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The catalytic desulfonylation of arenesulfonyl chlorides and bromides by $RhCl(PPh_3)_3$ (1), $RhCl(CO)(PPh_3)_2$ (2), $IrCl(CO)(PPh_3)_2$ (3), $RuCl_2(PPh_3)_3$ (4), $Pt(PPh_3)_4$ (5), and $PdCl_2$ (6) has been investigated. The desulfonylation is assumed to proceed mainly by a metal ion promoted mechanism and to a smaller extent *via* homolytic decomposition. A theory of the former mechanism has been suggested which accounts for the observations made in this study. The essential features of the theory are the steps $ArSO_2IrCl_2(CO)(PPh_3)_2$ (7) → $ArSO_2IrCl_2(CO)(PPh_3)$ (8) → $ArIrCl_2(CO)(SO_2)(PPh_3)$ (9) and loss of sulfur dioxide from the last compound. Several new rhodium and iridium complexes are described.

In a preliminary communication[1] we reported that chlorotris(triphenylphosphine)rhodium(I), $RhCl(PPh_3)_3$ (1), catalyzes the conversion of arenesulfonyl chlorides into the corresponding aryl chlorides.

We have studied now the applicability of this homogeneous catalytic desulfonylation to a variety of aromatic sulfonyl halides, using various complexes of the platinum group (Tables I and II) as catalysts. In addition, we investigated the nature of some catalyst–substrate complexes that are assumed to be intermediates in the process.

carbonylbis(triphenylphosphine)iridium(I), $IrCl(CO)(PPh_3)_2$ (3), dichlorotris(triphenylphosphine)ruthenium(II), $RuCl_2(PPh_3)_3$ (4), tetrakis(triphenylphosphine) platinum(0), $Pt(PPh_3)_4$ (5), and palladium dichloride (6) were used, the undesired side reactions became more and more predominant.

The homolytic decomposition could generally be reduced by dilution of the reaction mixture with hexachlorobenzene.

In Table II some representative experiments using 1 as catalyst are summarized. The results obtained with

TABLE I

DESULFONYLATION OF BENZENE- AND *p*-CHLOROBENZENESULFONYL CHLORIDE BY VARIOUS CATALYSTS

Sulfonyl chloride	Wt, g	Catalyst	Method[a]	Maximum yield of pure aryl halide, %
Benzene-	17.6	$RhCl(PPh_3)_3$ (1)	A	79
Benzene-	15	$RhCl(PPh_3)_3$ (1)	B	88
Benzene-	5	$RhCl(PPh_3)_3$ (1)	C	75
Benzene-	10.7	*trans*-$RhCl(CO)(PPh_3)_2$ (2)	A	32
Benzene	5	*trans*-$RhCl(CO)(PPh_3)_2$ (2)	C	59
Benzene-	15	*trans*-$IrCl(CO)(PPh_3)_2$ (3)	A	36
Benzene-	17.2	*trans*-$IrCl(CO)(PPh_3)_2$ (3)	C	74
Benzene-	10	$RuCl_2(PPh_3)_3$ (4)	B	37
Benzene-	5.5	$RuCl_2(PPh_3)_3$ (4)	C	50
Benzene-	10	$Pt(PPh_3)_4$ (5)	B	20
Benzene-	10.6	$Pt(PPh_3)_4$ (5)	C	50
Benzene-	10.4	$PdCl_2$ (6)	A	27
Benzene-	10	$PdCl_2$ (6)	C	65
p-Chlorobenzene-	10	$RhCl(PPh_3)_3$ (1)	A	85
p-Chlorobenzene-	15	$RhCl(PPh_3)_3$ (1)	B	67
p-Chlorobenzene-	5	$RhCl(PPh_3)_3$ (1)	C	97
p-Chlorobenzene-	10	*trans*-$RhCl(CO)(PPh_3)_2$ (2)	A	35
p-Chlorobenzene-	10	*trans*-$RhCl(CO)(PPh_3)_2$ (2)	C	71
p-Chlorobenzene-	10	*trans*-$IrCl(CO)(PPh_3)_2$ (3)	A	37
p-Chlorobenzene-	14.2	*trans*-$IrCl(CO)(PPh_3)_2$ (3)	C	74
p-Chlorobenzene-	15	$RuCl_2(PPh_3)_3$ (4)	B	55
p-Chlorobenzene-	5	$RuCl_2(PPh_3)_3$ (4)	C	60
p-Chlorobenzene-	15	$Pt(PPh_3)_4$ (5)	B	46
p-Chlorobenzene-	5	$Pt(PPh_3)_4$ (5)	C	55

[a] See Experimental Section: A, simple distillation; B, under nitrogen; C, in hexachlorobenzene.

In Table I, the results obtained with benzene- and *p*-chlorobenzenesulfonyl chloride and several catalysts are summarized. The figures indicate that the rhodium complex 1 is the best of these catalysts: the rate of desulfonylation is high in comparison with that of the competing homolytic noncatalytic decomposition of the sulfonyl chlorides.[2] When chlorocarbonylbis(triphenylphosphine)rhodium(I), $RhCl(CO)(PPh_3)_2$ (2), chlorosimple derivatives of benzenesulfonyl chloride and bromide are comparable with those obtained by heterogeneous catalyses.[3]

In these cases the noncatalyzed thermal decomposition is slow and the desulfonylation is believed to

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TABLE II

DESULFONYLATION OF ARENESULFONYL HALIDES BY 1

Expt	Sulfonyl halide (g)	Method[a]	Reaction time, min	Aryl halides formed (best yield obtained, %)
1	$C_6H_5SO_2Br$ (4.7)	C	5	C_6H_5Br (60)
2	p-$CH_3C_6H_4SO_2F$ (15)	A, D	180	No aryl fluoride
3	p-$CH_3C_6H_4SO_2Cl$ (15)	A	30	p-$ClC_6H_4CH_3$ (72)
4	p-$CH_3C_6H_4SO_2Br$ (7)	A	5	No aryl bromide
5	p-$CH_3C_6H_4SO_2Br$ (27)	C	5	p-$BrC_6H_4CH_3$ (45) p-$ClC_6H_4CH_3$ (traces)
6	2,4,6-$(CH_3)_3C_6H_2SO_2Cl$ (3)	C	4	2-Chloromesitylene (27)
7	p-$CH_3OC_6H_4SO_2Cl$ (15)	A	40	p-$ClC_6H_4OCH_3$ (40)
8	p-$FC_6H_4SO_2Cl$ (15)	A	240	p-ClC_6H_4F (61)
9	p-$FC_6H_4SO_2Br$ (3.9)	C	15	p-BrC_6H_4F (50), p-ClC_6H_4F (traces)
10	p-$ClC_6H_4SO_2F$ (4)	D	330	p-ClC_6H_4F (traces)
11	2,5-$Cl_2C_6H_3SO_2Cl$ (10)	A	25	1,2,5-$C_6H_3Cl_3$ (65)
12	p-$BrC_6H_5SO_2Cl$ (15)	A, B	20	p-$C_6H_4Cl_2$ (18) p-BrC_6H_4Cl (34) p-$C_6H_4Br_2$ (17)
13	p-$BrC_6H_4SO_2Cl$ (3)[b]	C	20	p-$C_6H_4Cl_2$ (8) p-BrC_6H_4Cl (14) p-$C_6H_4Br_2$ (3)
14	p-$BrC_6H_4SO_2Cl$ (3)[c]	D	20	p-$C_6H_4Cl_2$ (6.5) p-BrC_6H_4Cl (9) p-$C_6H_4Br_2$ (2.8)
15	p-$BrC_6H_4SO_2Br$ (3)[d]	A	7	p-$C_6H_4Br_2$ (60)
16	p-$BrC_6H_4SO_2Br$ (3)[e]	C	20	p-$C_6H_4Cl_2$ (12) p-BrC_6H_4Cl (32) p-$C_6H_4Br_2$ (29)
17	p-$IC_6H_4SO_2Cl$ (10)[f]	C	15	p-$C_6H_4Cl_2$ (6), p-ClC_6H_4I (29) p-$C_6H_4I_2$ (16)
18	o-$O_2NC_6H_4SO_2Cl$ (5)	D	90	o-$ClC_6H_4NO_2$ (3)
19	m-$C_6H_4(SO_2Cl)_2$ (10)	A	15	m-$C_6H_4Cl_2$ (62)
20	1,3,5-$C_6H_3(SO_2Cl)_3$ (3)	A	10	1,3,5-$C_6H_3Cl_3$ (33)
21	α-$C_{10}H_7SO_2Cl$ (5)	A	30	α-$C_{10}H_7Cl$ (17)
22	β-$C_{10}H_7SO_2F$ (10)	D	180	β-$C_{10}H_7F$ (10)
23	β-$C_{10}H_7SO_2Cl$ (6)	A[g]	20	β-$C_{10}H_7Cl$ (69)
24	β-$C_{10}H_7SO_2Cl$ (5)	D	30	β-$C_{10}H_7Cl$ (53)
25	4-$FC_{10}H_6$-1-SO_2Cl (5)	A[g]	20	1-$ClC_{10}H_6$-4-F (70)
26	8-$ClC_{10}H_6$-1-SO_2Cl (4)	D	20	1,8-$C_{10}H_6Cl_2$ (27)
27	2-Fluorenesulfonyl chloride (0.9)	D[h]	10	2-Chlorofluorene (6)
28	1-Anthracenesulfonyl chloride (2.9)	D	10	1-Chloroanthracene (9)
29	6-Chrysenesulfonyl fluoride (1.3)	D	270	6-Fluorochrysene (traces)
30	6-Chrysenesulfonyl chloride (2)[i]	D	15	6-Chlorochrysene (50)

[a] See Experimental Section: A, B, and C as in Table I; D, in hexachlorobenzene but under reflux. [b] When **3** was used as catalyst, the products and yields were as follows: p-$C_6H_4Cl_2$ (3); p-BrC_6H_4Cl (18); p-$C_6H_4Br_2$ (6). [c] In the absence of catalyst: p-$C_6H_4Cl_2$ (12); p-BrC_6H_4Cl (11); p-$C_6H_4Br_2$ (2). [d] In the absence of catalyst, 40%. [e] In the absence of catalyst: p-$C_6H_4Cl_2$ (1); p-BrC_6H_4Cl (16); p-$C_6H_4Br_2$ (30). [f] Similar results were obtained without catalyst. [g] The reaction was carried out under reduced pressure, which permits the reaction mixture to boil between 255 and 275°. [h] Under nitrogen. [i] In the absence of catalyst 6.5% 6-chlorochrysene was formed.

proceed mainly by metal-ion promotion. The sulfonyl halides of lower stability, *i.e.*, those that split homolytically at, or below, the threshold temperature for *catalytic* desulfonylation,[1] give lower yields of the expected aryl halides.

The sulfonyl bromides belong to the latter category and do not yield aryl bromides by simple distillation over the catalyst (method A), but dilution of the reaction mixtures with a tenfold excess of hexachlorobenzene (method C) permits the formation of the aryl bromides (expt 1, 5, and 9).

That the desulfonylation of the sulfonyl bromides proceeds, at least to a small extent, by a free-radical mechanism is shown by the fact that both p-toluene- and p-fluorobenzenesulfonyl bromide react with the perchlorinated solvent and form small quantities of p-chlorotoluene and p-dichlorobenzene, respectively. Moreover, when p-bromobenzenesulfonyl bromide—whose tendency to undergo homolytic decomposition is also shown below—is heated with **1** in perfluorobiphenyl or in Perfluoroalkane-225 (Peninsular ChemResearch Inc.), fluorobenzene and p-bromofluorobenzene are formed along with the expected p-dibromobenzene.

While fluoro- and chlorobenzenesulfonyl chloride do not decompose thermally in the absence of the catalyst to a considerable extent, the bromo and especially the

TABLE III
PHYSICAL DATA AND ANALYSES FOR IRIDIUM AND RHODIUM COMPOUNDS

Compd	Approx mp, °C dec	C, % Found	C, % Calcd	H, % Found	H, % Calcd	Cl, % Found	Cl, % Calcd	P, % Found	P, % Calcd	S, % Found	S, % Calcd	ν_{CO}[a] cm^{-1}
$C_{44}H_{37}Cl_2IrO_3P_2S$ (**7**, Ar = *p*-$CH_3C_6H_4$)[b]	290	53.9	53.4	3.7	3.8			6.9	6.4	3.7	3.3	2080
$C_{26}H_{22}Cl_2IrO_3PS$ (**8** or **9**, Ar = *p*-$CH_3C_6H_4$)	260	43.9	44.1	3.5	3.1	10.0	10.0	4.4	4.4	4.2	4.5	2098
$C_{43}H_{34}Cl_3IrO_3P_2S$ (**7**, Ar = *p*-ClC_6H_4)[b]	205	52.1	52.2	4.4	3.4	11.4	10.8			3.7	3.2	2080
$C_{25}H_{19}Cl_3IrO_3PS$ (**8** or **9**, Ar = *p*-ClC_6H_4)	250	41.3	41.2	2.8	2.6	14.4	14.6	4.2	4.3	4.0	4.4	2090
$C_{43}H_{34}Cl_3IrOP_2$ (**11**, Ar = *p*-ClC_6H_4)	285	55.4	55.7	3.6	3.7	12.3	12.5	6.5	6.7	0.0	0.0	2020
$C_{25}H_{19}Cl_2IrO_3PS$ (**12** or **13**, Ar = *p*-ClC_6H_4)[c]	200	43.8	43.3	2.8	2.7			4.6	4.5	4.5	4.6	2105
$C_{50}H_{38}Cl_6Ir_2O_4P_2S$ (**14**)[c]	282	43.4	43.1	2.8	2.7	15.0	15.4			2.7	2.3	2040 br
$C_{47}H_{37}Cl_2IrO_3P_2S$ (**7**, Ar = β-$C_{10}H_7$)	210	55.9	56.0	3.7	3.7	7.5	7.1	6.5	6.2			2080
$C_{29}H_{22}Cl_2IrOP$ (**10**, Ar = β-$C_{10}H_7$)	>300	51.6	51.1	3.3	3.2	10.0	10.4	4.4	4.7	0.0	0.0	2070
$C_{29}H_{22}ClIrO_3PS$ (**12** or **13**, Ar = β-$C_{10}H_7$)[c]	>300	49.0	49.0	3.3	3.1	5.2	5.0	4.3	4.3	4.4	4.4	2050
$C_{35}H_{28}Cl_2IrO_3PS$ (**15**)		51.1	51.2	3.3	3.4			3.8	3.8	4.1	3.9	2095
$C_{47}H_{37}ClFIrO_3P_2S$ (**16**)	204	56.8	56.9	3.9	3.7			6.1	6.3	3.0	3.2	2080
$C_{25}H_{22}Cl_2O_2PRhS$ (**17**, Ar = *p*-$CH_3C_6H_4$)	283	51.0	50.8	3.7	3.7	12.4	12.0	5.2	5.2			
$C_{28}H_{22}Cl_2O_2PRhS$ (**17**, Ar = β-$C_{10}H_7$)	218	53.5	53.5	4.2	3.5	11.6	11.3	4.6	4.9			

[a] In Nujol. [b] *Cf.* ref 6. [c] Paramagnetic.

iodo derivatives undergo extensive homolytic fragmentation at their boiling points. Thus, *e.g.*, *p*-bromobenzenesulfonyl chloride is converted after 20 min at reflux into 0.4% *p*-dichlorobenzene, 12% *p*-bromochlorobenzene, and 8.5% *p*-dibromobenzene, and in the presence of hexachlorobenzene to 12, 11, and 2% of these dihalides, respectively. Addition of catalytic amounts of either **1** or **3** lowers the degree of interaction with the solvent (expt 13 and 14). The formation of *p*-dichloro- and *p*-dibromobenzene does not result from disproportionation of *p*-bromochlorobenzene, as the latter is unaffected by **1**. Similar radical-type disproportionation and interaction with the solvent were observed with *p*-bromobenzenesulfonyl bromide (expt 15 and 16).

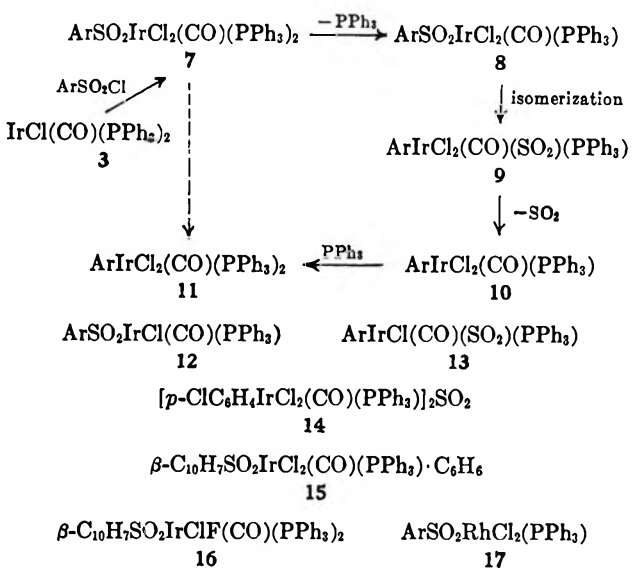
Arenedi- and -trisulfonyl chlorides are desulfonylated at 240–250° in fair yields (expt 19 and 20), while higher temperatures lead to extensive polymerization.

Naphthalenesulfonyl chlorides could be converted catalytically into the corresponding chloronaphthalenes when the reaction temperature was carefully controlled (below 275°). The polycyclic sulfonyl chlorides are polymerized by **1**, when heated in the absence of hexachlorobenzene, while in the presence of this solvent some quantities of the polycyclic aryl chlorides are formed. 6-Chrysenesulfonyl chloride is exceptional in that it yields up to 50% 6-chlorochrysene together with varying amounts of chrysene (up to 36%). Thermal decomposition of 6-chrysenesulfonyl chloride (without **1**) gave up to 6.5% aryl halide.

The desulfonylation of sulfonyl fluorides, which has been reported to be successful in some heterogeneous catalyses,[3] generally failed under our experimental conditions: benzene- and *p*-toluenesulfonyl fluoride did not give any fluorides on refluxing with **1** for many hours. *p*-Chlorobenzene- and 6-chrysenesulfonyl fluoride yielded up to 2% the expected fluoride, probably as a result of homolytic fission, and 2-naphthalenesulfonyl fluoride could be converted into 2-fluoronaphthalene in 10% yield.

Following our experience in the field of catalytic decarbonylation,[4] we attempted to study the mechanism of the catalytic desulfonylation by treating several sulfonyl halides with the catalysts at various temperatures between 78 and 160°. The rhodium catalyst **1** gave only a small number of defined addition complexes, one, $Rh_2Cl_2(SO_2)(PPh_3)_2$,[1] being an adduct of sulfur dioxide and dissociated **1** [*cf.* the formation of $RhCl(SO_2)(PPh_3)_2$ directly from **1** and liquid sulfur dioxide].[5] The Vaska complex $IrCl(CO)(PPh_3)_2$ (**3**) that has been shown above to catalyze the desulfonylation reaction (though less effectively than **1**), however, reacts smoothly with several sulfonyl halides to give the 12 complexes listed in Table III.

In a previous study, Collman and Roper[6] reported that a number of sulfonyl chlorides react with **3** to give iridium sulfinate complexes of type **7**, two of which (Ar = C_6H_5 and Ar = *p*-$CH_3C_6H_4$) could be transformed into **11** by heating at 110°. It could thus be assumed that the conversion of arenesulfonyl halides into aryl halides is based on this simple reaction **7** → **11**. However, while the analogous decarbonylation reaction of, *e.g.*, $CH_3COIrBr_2(CO)(PPhEt_2)_2$ to $CH_3IrBr_2(CO)(PPhEt_2)_2$,[7] and the desulfonylation of some platinum(0) sulfinate complexes[8] could be rationalized as one- and two-step processes, respectively, the direct



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desulfonylation of **7** seems improbable (unless a seven-coordinated iridium intermediate were formed), and our experiments provide evidence that the transformation **7** → **11** is a multistep process. Initial loss of PPh_3 yields **8**, which isomerizes to **9** and by loss of SO_2 gives **10**. The latter recombines with PPh_3 to give aryldichlorocarbonylbis(triphenylphosphine)iridium (**11**).

In our experience *p*-toluene-, *p*-chlorobenzene-, and β-naphthalenesulfonyl chloride reacted with **3** in aromatic hydrocarbons to give complexes of type **7** only in very poor yields and in an impure state. The main products in these reactions were complexes of type **8** (or **9**). β-Naphthalenesulfonyl chloride in benzene gave the benzene solvate **15**. Addition of triphenylphosphine to the reaction mixture led, however, in all cases to reasonable yields of **7**.

The reaction of **3** with equimolar quantities (or with a small excess) of β-naphthalenesulfonyl chloride in boiling benzene led to the formation of the desulfonylated complex **10**. *p*-Chlorobenzenesulfonyl chloride gave under these conditions a divalent iridium compound of structure **12** (or **13**), which may arise from **8** (or **9**) by loss of a chlorine atom. The analogous β-naphthyliridium(II) compound crystallized from the boiling mixture of equimolar amounts of **3** and β-naphthalenesulfonyl chloride in mesitylene.

The analyses of several complexes isolated show an S to Ir ratio of 1:2. The formation of such compounds—one of which is **14**—is easily rationalized by the reaction pathway described above.

It is noteworthy that from the reaction mixture of chloride-free β-naphthalenesulfonyl *fluoride*, **3**, and PPh_3 in boiling mesitylene, some dichlorosulfinate, **7** (Ar = β-$C_{10}H_7$), was isolated in addition to the expected fluoro compound **16**. The complexity of the reaction, including the extensive ligand exchange, is evidenced by the fact that upon concentration of the mother liquor from this reaction, we obtained a mixture showing six distinctive M–CO bands in the infrared.

The rhodium analog of **3**, chlorocarbonylbis(triphenylphosphine)rhodium (**2**), gave with the sulfonyl chlorides complex mixtures. Two compounds which could be separated in fairly pure state, *viz.* **17**, Ar = *p*-$CH_3C_6H_4$, and **17**, Ar = β-$C_{10}H_7$, surprisingly, had lost the CO group. The desulfonylation of the probable initial rhodium–sulfinate complex $ArSO_2RhCl_2(CO)(PPh_3)_2$ might thus proceed either after extrusion of one molecule of PPh_3 or, alternatively, by loss of carbon monoxide in the well-known decarbonylation pathway.

In conclusion, we feel that although not all complexes isolated in this study are necessarily intermediates in the *catalytic* desulfonylation, and, although catalysts **1**, **2**, **4**, **5**, and **6** might react differently from **3**, the essential features of the catalysis are the formation of a metal–sulfinate complex and loss of SO_2. Elimination of ArX and recombination of the remaining metal compound with the sulfonyl halide then concludes the catalytic cycle.

Experimental Section

Chlorotris(triphenylphosphine)rhodium(I) (**1**),[9] *trans*-chlorocarbonylbis(triphenylphosphine)rhodium(I) (**2**),[10] *trans*-chlorocarbonylbis(triphenylphosphine)iridium(I) (**3**),[10,11] dichlorotris(triphenylphosphine)ruthenium(II) (**4**),[12] and tetrakis(triphenylphosphine)platinum(0) (**5**)[13] have been prepared by methods described in the literature. The different methods used for the desulfonylation reactions (see Tables I and II) are illustrated by the following examples.

Method A. *p*-Dichlorobenzene from *p*-Chlorobenzenesulfonyl Chloride.—A mixture of 10.0 g of freshly distilled *p*-chlorobenzenesulfonyl chloride and 0.1 g of chlorotris(triphenylphosphine)-rhodium(I) (**1**) was heated in a Claisen flask equipped with a 25-cm-long Vigreux column, so as to permit distillation at 166–172° of the *p*-dichlorobenzene formed. After 25 min no more of this compound was collected; a polymer remained in the distillation flask. The crude distillate was taken up with methylene chloride and the solution was washed with alkali, neutralized, dried, and distilled, yield 5.9 g (85%) of pure *p*-dichlorobenzene, mp 53°, bp 168°.

Method B. Chlorobenzene from Benzenesulfonyl Chloride.—A slow stream of nitrogen was passed through the system described above, in which a mixture of 10.0 g of freshly distilled benzenesulfonyl chloride and 0.1 g of dichlorotris(triphenylphosphine)ruthenium(II) (**4**) was heated at 240° (wax bath). Chlorobenzene distilled over during 75 min, and much polymer was left in the flask. The distillate was worked up as above, yielding 2.35 g (37%) of pure chlorobenzene, bp 131°.

Method C. *p*-Bromofluorobenzene from *p*-Fluorobenzenesulfonyl Bromide.—In the same apparatus as in method A, there was placed 3.9 g of *p*-fluorobenzenesulfonyl bromide (see below), 60 mg of **1**, and 12 g of purified hexachlorobenzene. Upon gentle heating 2.2 g of material distilled, which was worked up in the usual manner. The crude product was analyzed by vapor phase chromatography on a 2 m × 6.4 mm column packed with 20% SE-30 on Chromosorb W and on a 1 m × 6.4 mm column packed with 10% Apiezon L on Chromosorb W, and was found to contain traces of fluorobenzene and 0.5% *p*-chlorofluorobenzene. The yield of *p*-bromofluorobenzene was 47%.

Method D. Desulfonylation of β-Naphthalenesulfonyl Fluoride.—A mixture of 10.0 g of *chloride-free* β-naphthalenesulfonyl fluoride (prepared in 90% yield from the sulfonyl *chloride* and potassium fluoride[14]), 20 g of hexachlorobenzene, and 125 mg of **1** was heated with stirring at 260° (wax bath) for 3 hr. The powdered reaction mixture was digested with 100 ml of hot benzene, filtered, and concentrated. The residue was freed from hexachlorobenzene by extraction with methanol. Vapor phase chromatography analysis on a 2.6-m-long column packed with 10% Apiezon L on Chromosorb W (condition for separation of naphthalene and 2-fluoronaphthalene) showed that 10% 2-fluoronaphthalene had been formed.

***p*-Fluorobenzenesulfonyl Bromide.**—A stirred mixture of 29.8 g of sodium *p*-fluorobenzenesulfonate, 27.1 g of red phosphorus, and 16 g of bromine was heated on the water bath until a homogeneous liquid was formed. After cooling, the reaction mixture was poured onto crushed ice and chloroform. The organic layer was washed with cold water, dried, and concentrated. The residue was distilled at 66° (0.1 mm), affording 13 g (54%) of *p*-fluorobenzenesulfonyl bromide as a colorless oil that darkened upon exposure to air.

Anal. Calcd for $C_6H_4FBrO_2S$: C, 30.1; H, 1.7; F, 7.9. Found: C, 30.1; H, 1.6; F, 7.9.

6-Chrysenesulfonyl Fluoride.—To a stirred solution of 5 g of chrysene in 200 ml of chloroform, 15 ml of fluorosulfonic acid was added at −50 to −20° during 75 min. The cold bath was removed and stirring was continued for 22 hr at room temperature. Crushed ice and chloroform were added and the organic layer was separated, washed several times with cold water, and dried. The solvent was removed and the oily residue was triturated with a mixture of chloroform and hexane. Thus 2.1 g (31%) of 6-chrysenesulfonyl fluoride, mp 175–179° (from cyclohexane), was obtained.

Anal. Calcd for $C_{18}H_{11}FO_2S$: C, 69.6; H, 3.6; F, 6.1. Found: C, 69.9; H, 3.1; F, 6.0.

Dichlorocarbonyl-*p*-tolylsulfinatobis(triphenylphosphine)iridium(III) (7, Ar = *p*-$CH_3C_6H_4$).—A stirred mixture of 600 mg of *p*-toluenesulfonyl chloride, 300 mg of **3**, 1.1 g of triphenyl-

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phosphine, and 20 ml of benzene was refluxed under nitrogen for 7 hr. The precipitate was filtered and successively washed with hot ethanol and hot acetone to yield the pale yellow complex: mp 290° dec, $\bar{\nu}^{Nujol}$ 1070 and 1230 (SO) and 2080 cm^{-1} (CO). The compound could not be freed from traces of impurities having bands at 1040, 1170, 1190, and 2020 cm^{-1}.

Dichlorocarbonyl-*p*-tolylsulfinato(triphenylphosphine)iridium(III) (**8**, Ar = *p*-$CH_3C_6H_4$).—A solution of 600 mg of *p*-toluenesulfonyl chloride and 310 mg of **3** in 20 ml of benzene was refluxed for 7 hr, and the light tan crystals which separated were filtered off and washed with cold acetone to yield a cream-colored complex that darkened at 220° and melted with decomposition at 259–260°, $\bar{\nu}^{Nujol}$ 1070 and 1268 (SO) and 2095 cm^{-1} (CO).

Reactions of *p*-Chlorobenzenesulfonyl Chloride and 3 in Benzene. A.—A stirred solution of 500 mg of *p*-chlorobenzenesulfonyl chloride and 400 mg of **3** in 40 ml of benzene was refluxed under nitrogen for 90 min. From the clear solution, a few crystals separated. They were filtered off and washed with hot acetone and proved to be **dichlorocarbonyl-*p*-chlorophenylsulfinatobis(triphenylphosphine)iridium(III)** (**7**, Ar = *p*-ClC_6H_4): mp 205° dec; $\bar{\nu}^{Nujol}$ 1062, 1220, and 1238 (SO) and 2080 cm^{-1} (CO). The *filtrate* was treated with light petroleum ether (bp 40–60°) and the voluminous precipitate was filtered and recrystallized several times from a mixture of benzene and cyclohexane, yielding light tan crystals of **chlorocarbonyl-*p*-chlorophenylsulfinato(triphenylphosphine)iridium(II)** (**12**, Ar = *p*-ClC_6H_4), mp 200°. In the esr measurement of the solid sample a very strong signal at $g = 2.03$ was observed.

B.—On refluxing a mixture of 600 mg of *p*-chlorobenzenesulfonyl chloride, 300 mg of 3 and 1.1 g of triphenylphosphine in 20 ml of benzene, a precipitate was formed, which was filtered off and treated with hot acetone. The pale yellow, *insoluble* **dichlorocarbonyl-*p*-chlorophenylbis(triphenylphosphine)iridium(III)** (**11**, Ar = *p*-ClC_6H_4) thus obtained decomposed at 285°.

Reaction of *p*-Chlorobenzenesulfonyl Chloride and 3 in Mesitylene.—*p*-Chlorobenzenesulfonyl chloride (600 mg) and 300 mg of **3** were heated in 20 ml of mesitylene at 80° for 90 min. Then the temperature was gradually raised to 160°. A solid separated, and the mixture was refluxed for an additional 3 hr. The precipitate was treated with boiling toluene. The *least soluble*, colorless fraction proved to be **dichlorocarbonyl-*p*-chlorophenylsulfinato(triphenylphosphine)iridium(III)** (**8**, Ar = *p*-ClC_6H_4). It turns deep yellow at 246° and decomposes at 250°: $\bar{\nu}^{Nujol}$ 1073, 1235, and 1263 (SO) and 2090 cm^{-1} (CO).

The fraction *soluble* in toluene was treated with petroleum ether (bp 40–60°) and recrystallized from benzene and cyclohexane, giving the correct analysis for **14**, mp 280–285° dec. The solid sample gave a signal at $g = 2.03$ in the esr spectrum.

Dichlorocarbonyl-β-naphthylsulfinato(triphenylphosphine)iridium(III)·C_6H_6 (**15**).—A mixture of 600 mg of β-naphthalenesulfonyl chloride, 300 mg of **3**, and 15 ml of benzene was refluxed with stirring. The mixture soon became homogeneous, and then a heavy precipitate was formed. After 5.5 hr the solid was filtered and washed with acetone to yield pale yellow crystals of **15**: $\bar{\nu}^{Nujol}$ 1085 and 1265 (SO) and 2095 (CO) cm^{-1}.

Dichlorocarbonyl-β-naphthyl(triphenylphosphine)iridium(III) (**10**, Ar = β-$C_{10}H_7$).—A solution of 182 mg of β-naphthalenesulfonyl chloride, 300 mg of **3**, and 20 ml of toluene was refluxed for 6 hr. (Alternatively, 20 ml of benzene was used and the mixture was refluxed for 11 hr.) The solution was diluted with hexane and the precipitate formed was refluxed with benzene for 5 min. The insoluble pale green crystals were sulfur-free and did not melt below 300°.

Chlorocarbonyl-β-naphthylsulfinato(triphenylphosphine)iridium(II) (**12**, Ar = β-$C_{10}H_7$).—A mixture of 182 mg of β-naphthalenesulfonyl chloride, 300 mg of **3**, and 20 ml of benzene was refluxed for 11 hr under nitrogen. The precipitate was refluxed with benzene for 5 min. The greenish, insoluble crystals obtained did not melt below 300°: $\bar{\nu}^{Nujol}$ 1075, 1270, and 1280 (SO) and 2050 cm^{-1} (CO). In the esr spectrum of the solid sample a strong signal at $g = 2.03$ was observed.

Chlorocarbonylfluoro-β-naphthylsulfinatobis(triphenylphosphine)iridium(III) (**16**) was obtained when 600 mg of β-naphthalenesulfonyl fluoride, 300 mg of **3**, and 20 ml of benzene were refluxed under nitrogen for 10 hr. The insoluble material was freed from some **dichlorocarbonyl-β-naphthylsulfinatobis(triphenylphosphine)iridium(III)** (**7**, Ar = β-$C_{10}H_7$) by heating with a mixture of benzene and acetone in which the latter is insoluble. This dichloro complex, mp 210°, was identical with a sample obtained by a procedure similar to that described for **7**, Ar = *p*-$CH_3C_6H_4$. The insoluble fluoro compound melted at 204°.

Dichloro-*p*-tolylsulfinato(triphenylphosphine)rhodium(III) (**17**, Ar = *p*-$CH_3C_6H_4$).—A mixture of 170 mg of *p*-toluenesulfonyl chloride, 300 mg of chlorocarbonylbis(triphenylphosphine)rhodium(I) (**2**), and 20 ml of benzene was refluxed under nitrogen for 3 hr. The orange precipitate did not dissolve in benzene and had no carbonyl bands in the infrared spectrum, mp 280–285°.

The soluble fraction proved to be a mixture of carbonyl-containing rhodium compounds.

Dichloro-β-naphthylsulfinato(triphenylphosphine)rhodium(III) (**17**, Ar = β-$C_{10}H_7$) was obtained by the same procedure as an orange-brown solid, mp 218° dec.

Registry No.—**1**, 14694-95-2; **2**, 13938-94-8; **3**, 14871-41-1; **4**, 15529-49-4; **5**, 14221-02-4; **6**, 7647-10-1; **7**, Ar = *p*-$CH_3C_6H_4$, 15629-10-4; **7**, Ar = *p*-ClC_6H_4, 15712-63-7; **7**, Ar = β-$C_{10}H_7$, 23916-65-6; **8**, Ar = *p*-$CH_3C_6H_4$, 23916-66-7; **8**, Ar = *p*-ClC_6H_4, 23916-67-8; **9**, Ar = *p*-$CH_3C_6H_4$, 24012-12-2; **9**, Ar = *p*-ClC_6H_4, 24012-13-3; **10**, Ar = β-$C_{10}H_7$, 23957-31-5; **11**, Ar = *p*-ClC_6H_4, 23957-32-6; **12**, Ar = *p*-ClC_6H_4, 23916-68-9; **12**, Ar = β-$C_{10}H_7$, 23916-69-0; **13**, Ar = *p*-ClC_6H_4, 24012-14-4; **13**, Ar = β-$C_{10}H_7$, 24012-15-5; **14**, 23957-33-7; **15**, 23916-70-3; **16**, 23916-71-4; **17**, Ar = *p*-$CH_3C_6H_4$, 24073-54-9; **17**, Ar = β-$C_{10}H_7$, 24035-14-1; 6-chrysenesulfonyl fluoride, 23924-10-9; benzenesulfonyl chloride, 98-09-9; *p*-chlorobenzenesulfonyl chloride, 98-60-2.

Acknowledgment.—We wish to thank Professor Ernst D. Bergmann for his advice in these studies.

Catalytic Hydrogenation. V.[1] The Reaction of Sodium Borohydride with Aqueous Nickel Salts. P-1 Nickel Boride, a Convenient, Highly Active Nickel Hydrogenation Catalyst

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The reaction of sodium borohydride with aqueous solutions of nickel salts immediately produces a finely divided black precipitate. This material (P-1 nickel) is a highly active catalyst for atmospheric pressure hydrogenations, more active than Raney nickel. The hydrogenations of a variety of alkenes have been examined and all but the most hindered double bonds were reduced successfully. Certain dienes were reduced cleanly to single olefinic products. P-1 nickel has marked advantages over Raney nickel: it is not pyrophoric; it is readily prepared *in situ;* it is highly reproducible.

During World War II Brown, Schlesinger, and coworkers[4] found that sodium borohydride reacted with certain first-row transition-metal salts to yield finely divided black precipitates, thought to be borides. The cobalt precipitate proved to have considerable activity as a catalyst for the hydrolysis of borohydride. In fact, the $NaBH_4$–cobalt system was investigated for the field generation of hydrogen.[5–7] Wartime pressure prevented further investigation of these black precipitates. However, in 1951 Paul and coworkers reported that the product of the reaction of nickel(II) salts with sodium borohydride was useful for catalytic hydrogenation. Activity was roughly equal to Raney nickel.[8,9]

We found that the reduction medium played an important role in the type of catalyst formed.[10,11] For example, in aqueous media a granular black material is formed from sodium borohydride and nickel(II) acetate. This material is at least as active as Raney nickel for double-bond hydrogenations.[10] However, in ethanol a nearly colloidal black suspension is produced which is much more sensitive to double-bond structure.[11,12] These materials, designated P-1 Ni and P-2 Ni, respectively,[13] are nonmagnetic and nonpyrophoric, unlike Raney nickel. Furthermore, they are easily reproducible and so readily prepared that detailed study of their characteristics as hydrogenation catalysts seemed warranted.

Therefore, as part of a systematic study of the uses of borohydride-reduced metal powders, we undertook a survey of hydrogenations using these nickel catalysts. This paper reports the results with P-1 Ni. A comparable study with P-2 Ni is in progress.

Results

The catalyst is prepared by treating an aqueous solution of nickel(II) salt with a threefold molar excess of sodium borohydride solution. After the excess borohydride has hydrolyzed, the water is decanted and the fine black granules are washed twice with absolute ethanol. We found that the presence of sodium acetate, sodium borate, ammonia, or sodium hydroxide during reduction had little effect on the activity of the catalyst for the hydrogenation of 1-octene. After reduction, two ethanol washings alone were sufficient. Washing of the catalyst with water, dilute acetic acid, dilute sodium hydroxide, or more ethanol had little or no effect on the activity.

Four nickel(II) salts were examined: nitrate, chloride, sulfate, and acetate. Nickel nitrate gave a precipitate which was too fine to be washed by decanting. Catalyst activity was slightly less for the chloride and sulfate than for the acetate, as shown by the times required for half-hydrogenation of cyclohexene: chloride, 22 min; sulfate, 18 min; acetate, 16 min. The acetate, $Ni(C_2H_3O_2)\cdot 4H_2O$, was chosen as standard. (In these studies 40 mmol of substrate and 5.0 mmol of catalyst was standard.)

Reproducibility was explored with the hydrogenation of 1-octene. In ten hydrogenations the time required for half-hydrogenation was between 6.0 and 7.0 min. During the course of the entire study, an occasional check run would require a maximum of 7.5 min for half-hydrogenation.

A comparison of the relative activity of the P-1 catalyst and W-2 Raney nickel[14] was made. The following results demonstrate the greater activity of P-1 nickel (olefin, relative time for half-hydrogenation of 40.0 mmol over P-1 nickel and W-2 Raney nickel): safrole, 1.0, 1.0; 1-octene, 1.0, 1.3; cyclopentene, 1.3, 2.0; cyclohexene, 2.5, 3.5; cyclooctene, 2.0, 5.3. These results are shown in detail in Table I.

The reaction plots for 1-octene show a noticeable, sharp decrease in rate toward the end. Glpc analysis at the rate break shows that only 2-octenes are present. Evidently the double bond isomerizes during hydrogenation; after the remaining 1-octene is consumed, 2-octenes

(1) Part IV: C. A. Brown, *Anal. Chem.*, **39**, 1882 (1967).
(2) National Science Foundation Postdoctoral Fellow, 1968–1969.
(3) Institute of Organic Chemistry, Syntex Research, 3401 Hillview Ave., Palo Alto, Calif. 94304.
(4) H. C. Brown, H. I. Schlesinger, A. E. Finholt, J. R. Gilbreath, H. R. Hoekstra, and E. K. Hyde, *J. Amer. Chem. Soc.*, **75**, 215 (1953).
(5) H. C. Brown, personal communication.
(6) For a detailed discussion of such a gas generator, see A. Levy, J. B. Brown, and C. J. Lyons, *Ind. Eng. Chem.*, **52**, 211 (1960).
(7) Later studies have shown that several platinum metals react with sodium borohydride to produce even more active catalysts for the hydrolysis: H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **84**, 1493 (1962).
(8) R. Paul, P. Buisson, and N. Joseph, *Compt. Rend.*, **232**, 627 (1951).
(9) R. Paul, P. Buisson, and N. Joseph, *Ind. Eng. Chem.*, **44**, 1006 (1952).
(10) C. A. Brown and H. C. Brown, *J. Amer. Chem. Soc.*, **85**, 1003 (1963).
(11) H. C. Brown and C. A. Brown, *ibid.*, **85**, 1004 (1963).
(12) (a) C. A. Brown, *Chem. Commun.*, 952 (1969); (b) C. A. Brown, research in progress.
(13) The designations are derived from Purdue University, where this work was initiated.
(14) A standard commercial sample of preformed Raney nickel was obtained from the Raney Catalyst Co., Inc., Chattanooga, Tenn. This catalyst is essentially the W-2 preparation and is that commonly stocked in many laboratories; thus it appeared representative. Although many preparations of Raney nickel have been reported, most procedures yield catalysts which differ little in activity in the hydrogenation of limonene: H. A. Smith, W. C. Bedoit, Jr., and J. R. Fuzek, *J. Amer. Chem. Soc.*, **71**, 3769 (1948).

TABLE I

HYDROGENATION OF REPRESENTATIVE OLEFINS OVER RANEY NICKEL AND P-1 NICKEL[a]

Olefin	Raney nickel[b] Initial[c] rate	Raney nickel[b] $t_{50\%}$,[d] min	P-1 nickel[b] Initial[c] rate	P-1 nickel[b] $t_{50\%}$,[d] min
Safrole	75	6	69	6
1-Octene	59	8	72	6
Cyclopentene	36	12	56	8
Cyclohexene	23	21	31	16
Cyclooctene	17	32	42	12

[a] Hydrogenation of 40.0 mmol of substrate over 5 mmol of catalyst in ethanol at 25° (1 atm). [b] P-1 nickel based upon amount of nickel acetate used in preparation. Raney nickel based on volume of settled catalyst, which weighed *ca.* 0.3 g when dry. [c] Average rate from 0 to 20% reaction, in cubic centimeters of H_2 at STP per minute. Total hydrogen uptake (STP) = 896 cm³. [d] Time for uptake of 20.0 mmol of hydrogen.

are hydrogenated at a slower rate.[15] The rate break occurs at an earlier point in the hydrogenation with Raney nickel, indicating more isomerization.

Isomerization during hydrogenation over the two catalysts was compared in the hydrogenations of 1-pentene. At 50% hydrogenation of 1-pentene, Raney nickel produced 3% *cis*- and 20% *trans*-2-pentene, a total of 23% isomerization. P-1 nickel produced 2% *cis*- and 5% *trans*-2-pentene, a total of 7%. The detailed comparison is shown in Table II.

TABLE II

ISOMERIZATION DURING HYDROGENATION OVER NICKEL CATALYSTS[a]

% Reaction	Product, mmol[b,c] *n*-Pentane	1-Pentene	*trans*-2-Pentene	*cis*-2-Pentene
	A. Raney nickel W-2			
0	0.0	40.0	0.0	0.0
25	9.2	24.8	4.0	1.6
50	20.4	10.4	8.0	1.2
75	30.4	0.0	7.2	2.4
	B. P-1 nickel			
0	0.0	40.0	0.0	0.0
25	9.6	28.8	1.2	0.4
50	20.3	16.6	2.0	0.8
75	30.6	4.4	3.3	1.7

[a] Hydrogenation of 40.0 mmol of 1-pentene over 5.0 mmol of nickel catalyst at 25° (1 atm). [b] By glpc. [c] Normalized. Absolute yields 90–100%.

Next, the effect of olefin structure upon hydrogenation over P-1 nickel was systematically investigated.

Effect of Chain Length.—Four olefins from C_5 to C_{12} were hydrogenated to determine what effect moderate changes in length might have. All were reduced smoothly, and the relative times for half-hydrogenation follow: 1-pentene, 1.2; 1-hexene, 1.0; 1-octene, 1.0; 1-dodecene, 1.2. In all cases breaks in rate owing to isomerization of the olefin (*vide supra*) occurred in the vicinity of 90% hydrogenation.

Effect of Chain Branching.—Successive substitutions of methyl groups for the hydrogens α to the double bond produced very little change in the relative times for half-hydrogenation: 1-pentene, 1.0; 3-methyl-1-butene, 1.25; 3,3-dimethyl-1-butene, 1.05. The larger value for 3-methyl-1-butene is probably an artifact of its low boiling point (20°) and high vapor pressure; at 25°, the reaction temperature, the hydrogen partial pressure in the reactor is undoubtedly significantly below atmospheric. The first two compounds exhibit a rate break around 85% reaction; the last had a linear rate (isomerization by a simple shift of a hydrogen atom is not possible).

(15) Similar double-bond migrations have been found with borohydride-reduced platinum metal catalysts: H. C. Brown and C. A. Brown, *Tetrahedron, Suppl. 8, Part I*, 129 (1966).

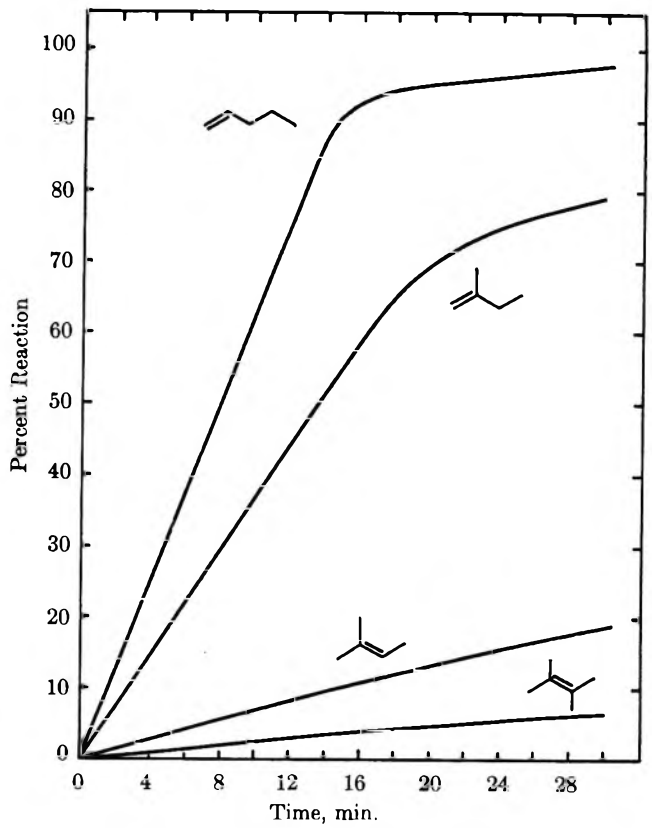


Figure 1.—Effect of substitution on rate of hydrogenation over P-1 nickel. Hydrogenation of 40.0 mmol of substrate over 5.0 mmol of catalyst at 25° (1 atm).

Effect of Increased Substitution.—Successively replacing the vinyl hydrogens with alkyl groups causes an appreciable decrease in reaction rate, as shown by the following relative half-hydrogenation times: 1-pentene, 1.0; 2-methyl-1-butene, 1.6; 2-methyl-2-butene, 16; 2,3-dimethyl-2-butene, *ca.* 45. Note that the big jump occurs between di- and trisubstitution. However, it is still significant that even the hindered tetrasubstituted olefin was still reduced under very mild conditions (25°, 1 atm). Figure 1 effectively demonstrates this effect of substitution.

Effect of Ring Size.—Cyclic olefins were readily reduced, with the order of reactivity being $C_5 > C_8 > C_6$. The relative times for half-hydrogenation follow: cyclopentene, 1.0; cyclooctene, 1.5; cyclohexene, 2.0 (1-octene, for comparison, is 0.8). The reactions slowed slightly toward the end. It is interesting to note that cyclohexene is the most reactive of these olefins over borohydride-reduced platinum metal catalysts.[15] Figure 2 reveals the effect of ring size on the rates of hydrogenation of cyclopentene, cyclohexene, and 1-octene over the two catalysts.

Phenyl Substituents.—Phenyl-substituted olefins are hydrogenated at least as readily as their aliphatic counterparts. For example, α-methylstyrene required only 70% as long as 2-methyl-1-butene for half-hy-

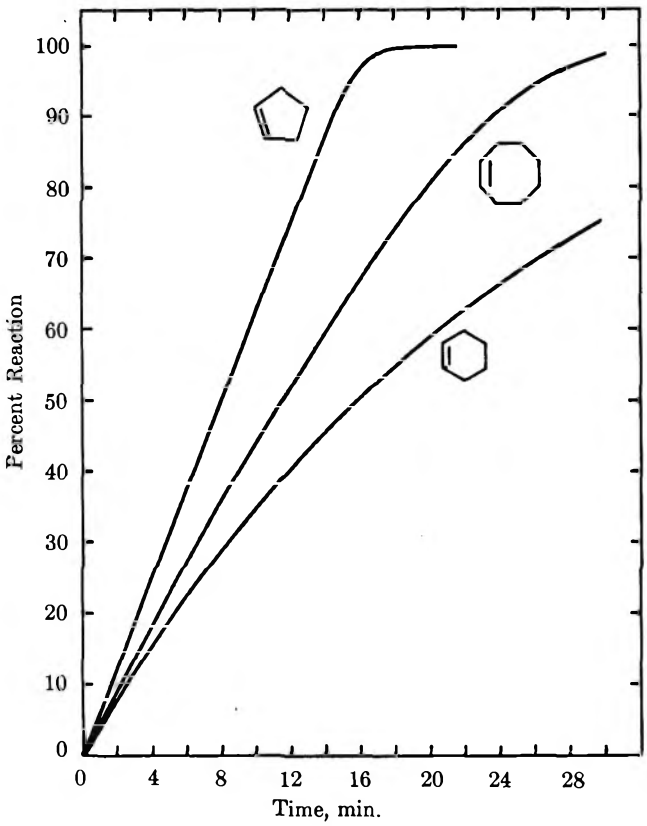


Figure 2.—Effect of ring size on rate of hydrogenation over P-1 nickel. Hydrogenation of 40.0 mmol of substrate over 5.0 mmol of catalyst at 25° (1 atm).

drogenation, while safrole took even less time than 1-octene. The relative half-hydrogenation times follow: safrole, 1.0; allyl benzene, 1.1; styrene, 1.2; α-methylstyrene, 1.6 (1-octene, 1.1).

Aromatic Nucleus.—In the cases above no evidence was found for reduction of the aromatic ring. In a separate experiment, benzene failed to reduce at all in 2 hr at atmospheric pressure and 25°. However, pyrocatechol is readily reduced to cyclohexanediol over P-1 Ni in an autoclave.[16]

The presence of benzene inhibits slightly the hydrogenation of simple olefins. Thus the addition of 40.0 mmol of benzene to the hydrogenation of 40.0 mmol of 1-octene resulted in an increase in half-hydrogenation time of 50% (10 min. *vs.* 6.5 min without benzene).

Effect of Bond Strain.—Reduction of norbornene proceeded smoothly and linearly. Time for half-hydrogenation was about 90% of that for 1-octene, and appreciably less than that for either cyclopentene or cyclohexene, its monocyclic analogs.

The above reductions are tabulated with initial rates and absolute half-hydrogenation times in Table III.

Selective Hydrogenations.—Applications of this catalyst to selective hydrogenations were generally beyond the scope of this study; they are under investigation currently. However, two selective hydrogenations can be reported: 2-methyl-1,5-hexadiene (I) and 4-vinylcyclohexene (II). After uptake of 1.0 equiv of hydrogen, glpc analysis showed that the vinyl group had been almost completely reduced in both

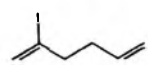
(16) G. Zweifel, University of California, Davis, personal communication.

TABLE III

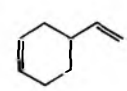
HYDROGENATION OF REPRESENTATIVE OLEFINS OVER THE P-1 NICKEL CATALYST[a]

Compd	Initial rate,[b] cm³ of H_2 at STP/min	$t_{50\%}$,[c] min
1-Pentene	56	8
1-Hexene	71	6.5
1-Octene	72	6
1-Dodecene	54	8
3-Methyl-1-butene	45	10
3,3-Dimethyl-1-butene	56	8.5
2-Methyl-1-butene	36	13
2-Methyl-2-butene	7	130
2,3-Dimethyl-2-butene	2	~360
Cyclopentene	56	8
Cyclohexene	31	16
Cyclooctene	43	12
Safrole[d]	72	6
Styrene[d]	63	7.5
α-Methylstyrene[d]	49	9.5
Allylbenzene[d]	69	6.5
Norbornene	80	6.0

[a] Hydrogenation of 40.0 mmol of substrate over 5.0 mmol of P-1 nickel in ethanol at 25° (1 atm). [b] Average rate from 0 to 20% reaction. Total reaction is 896 cm³ at STP. [c] Time for adsorption of 20 mmol of hydrogen. [d] Reduction of side chain only.



I



II

cases. Thus 2-methyl-1-hexene was obtained 93% pure, and 4-ethylcyclohexene 98% pure. Thus this catalyst does seem to have promise in this area.

Discussion

P-1 nickel is a very useful catalyst for a variety of carbon–carbon double bond hydrogenations. Even under the very mild reaction conditions employed in this study, only the hindered tri- and tetrasubstituted double bonds were sluggish. Increased hindrance α to the double bond does not seem to have much effect.

One point of some interest is the inhibition of 1-octene hydrogenation by benzene, even though benzene is not reduced noticeably under the typical reaction conditions. This suggests that the aromatic ring may physically adsorb onto the catalyst surface (interfering with olefin chemisorption) without actually bonding (chemisorbing) to the active metal sites. As noted, however, the use of more vigorous conditions (high pressure, elevated temperature) may permit the reduction of aromatic compounds.[16] Further work on this application is anticipated.

P-1 nickel is more active and produces less double-bond migration than standard Raney nickel. Furthermore, P-1 nickel is not pyrophoric.[17] It is also much more readily prepared than Raney nickel. The preparation of enough of the latter for a small-scale hydrogenation requires more than 1 hr. P-1 nickel may be prepared in 10–15 min merely by mixing two

(17) (a) In contrast, a literature preparation[17b] of W-2 Raney nickel warns that "the product [catalyst] is highly pyrophoric and must be kept under a liquid at all times;" (b) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 181.

reagents in the reactor.[18] Very possibly because P-1 nickel is always freshly prepared, we have realized consistently high reproducibility and reliability over a period of years and in several laboratories.

Extra activation of P-1 nickel-type catalysts have been reported by conducting the reduction of nickel salts in the presence of 2% chromium, molybdenum, tungsten, or vanadium salts.[9,19] Mears and Boudart[20] have shown that this increase in activity (as measured for dehydrogenation of isopropyl alcohol to acetone) is directly proportional to increases in catalyst surface area (presumably owing to the presence of a "foreign" material during catalyst precipitation).

In addition to high reproducibility, P-1 nickel is very resistant to poisoning in successive hydrogenations using the same batch of catalyst, considerably more so than Raney nickel.[9]

The nature of the catalyst itself remains unknown. The presence of boron has been shown by chemical analyses,[4,8,9,21] atomic absorption spectroscopy,[21] and electron-microprobe X-ray analysis (strong K_α line for boron).[21] The material was originally[4,8,9] postulated to be Ni_2B, formed as shown in eq 1. This reaction

$$2Ni(OAc)_2 + 4NaBH_4 + 9H_2O \longrightarrow Ni_2B + 4Na(OAc)_2 + 3B(OH)_3 + 12.5H_2(g) \quad (1)$$

yields 78% of the hydrogen theoretically obtainable from $4NaBH_4(\rightarrow 16.0\ H_2)$. In fact the yield of hydrogen is 75–78%.[22–24] Chemical analyses have indicated as much as 7.7% boron (8.5% calculated for Ni_2B).[8,9] However, the boron content has been reported to vary with the ratio of reactants used in preparation.[25]

Films produced by similar borohydride–nickel salt reactions in nonelectrolytic plating baths are reported to be amorphous mixtures of nickel and boron containing 3–10% of the latter. At temperatures over 400°, these films yield crystalline nickel borides.[26,27]

In addition to hydrogenation and dehydrogenation,[18] P-1 nickel (or similarly prepared materials) has been reported highly useful for deuterium exchange[28] and selective desulfurizations.[29,30]

The P-1 nickel catalyst and similar materials should find considerable use in organic syntheses. We are currently studying further properties of these highly accessible and interesting materials, both for hydrogenation and other reactions.

(18) (a) Because of the time consumed, the preparation of Raney nickel is often carried out on a large scale, or the catalyst is purchased in 1-lb containers.[14] However, catalysts change on aging (generally for the worse).[18b] (b) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1967.

(19) Similar activation has been reported for Raney nickel: R. Paul, *Bull. Soc. Chim. Fr.*, 208 (1946).

(20) D. E. Mears and M. Boudart, *Amer. Inst. Chem. Eng. J.*, **12**, 313 (1966).

(21) Ch.-Y. Chen, H. Yamamoto, and T. Kwan, *Chem. Pharm. Bull.* (Tokyo), **17**, 1287 (1969).

(22) C. A. Brown, unpublished observations.

(23) N. N. Mal'tseva, *et al.*, *Zh. Neorg. Khim.*, **11**, 720 (1966).

(24) N. N. Mal'tseva, *et al.*, *Dokl. Akad. Nauk SSSR*, **160**, 325 (1965).

(25) K. N. Mochalov, *et al.*, *Tr. Kazansk. Khim. Technol. Inst.*, **33**, 95 (1964); *Chem. Abstr.*, **64**, 18930g (1966).

(26) K. Lang, *Electroplating Metal Finishing*, **19**, 86 (1966).

(27) H. Narcus, *Plating*, **54**, 380 (1967)

(28) G. E. Colfand and J. L. Garnett, *J. Phys. Chem.*, **68**, 3887 (1964).

(29) W. E. Truce and F. E. Roberts, *J. Org. Chem.*, **28**, 961 (1963).

(30) W. E. Truce and F. M. Perry, *ibid.*, **30**, 1316 (1965).

Experimental Section

Apparatus.—The all-glass automatic borohydride hydrogenator described in earlier studies[1,31] was employed throughout.[32] This device greatly facilitates the preparation and use of P-1 nickel catalysts.

Reagents.—The following nickel salts were obtained from J. T. Baker Co. (Baker A.R. grade): $Ni(C_2H_3O_2)_2\cdot 4H_2O$; $NiCl_2\cdot 6H_2O$; $Ni(NO_3)_3\cdot 6H_2O$; $NiSO_4\cdot 6H_2O$.

Sodium borohydride, 98%, was produced and supplied by Ventron Corp. A stabilized solution for catalyst preparation is prepared by dissolving 1.0 g of sodium hydroxide and 9.45 g of sodium borohydride in 200 cm³ of water. This is diluted to 250 cm³ and filtered. It is best prepared freshly the day required.

The organic substrates were usually used directly from freshly opened bottles. If colored or if their refractive index varied significantly from literature values, they were distilled from sodium borohydride. Substrates and their sources are listed in Table IV.

Table IV

Substrates and Sources

Compd	Source
1-Pentene	Phillips[a]
1-Hexene	Phillips
1-Octene	Phillips
1-Dodecene	HW[b]
3-Methyl-1-butene	Phillips
3,3-Dimethyl-1-butene	API[c]
2-Methyl-1-butene	Phillips
2-Methyl-2-butene	Phillips
2,3-Dimethyl-2-butene	Phillips
Cyclopentene	Phillips
Cyclohexene	Phillips
Cyclooctene	CS[d]
Safrole	Aldrich[e]
Styrene	MCB[f]
α-Methylstyrene	MCB
Allylbenzene	Columbia[g]
Benzene	Phillips
4-Vinylcyclohexene	Phillips
2-Methyl-1,5-hexadiene	Columbia

[a] Phillips Petroleum Co. (Pure Grade). [b] Humphrey–Wilkens Co. [c] American Petroleum Institute project at The Ohio State University. [d] Cities Service Petroleum Co. [e] Aldrich Chemical Co. [f] Matheson Coleman and Bell. [g] Columbia Chemical Co.

Catalyst Preparation and Use.—Nickel acetate tetrahydrate (1.24 g, 5.0 mmol) was dissolved in 50 cm³ of water in a 125-ml erlenmeyer flask (modified for high-speed magnetic stirring). This flask was attached to the borohydride hydrogenator and flushed with nitrogen. With vigorous stirring 10.0 cm³ of 1.0 *M* sodium borohydride solution in 0.1 *M* sodium hydroxide (*vide supra*) was injected over 30–45 sec. When gas evolution ceased, a further 5.0 cm³ of solution was added. After gas evolution again subsided, stirring was discontinued and the flask was detached from the hydrogenator. The supernate was decanted from the catalyst (fine black granules); the catalyst was then washed twice with 50 cm³ of ethanol by swirling and decanting. Then $(50 - n)$ cm³ (n = volume of substrate to be added) of ethanol was added, the flask was attached to the hydrogenator, and the system was purged with hydrogen. Stirring was resumed and the reaction was initiated by injecting olefin.

Agitation was provided by a small LaPine magnetic stirrer and a 1.5-in. TFE-covered stirring bar fitted with an oversize spin ring.

Samples were withdrawn from reaction mixtures through an 8-mm port in the reactor closed with a serum stopper; using a syringe and stainless steel needle, 0.1-cm³ samples were pulled at appropriate points. Blank runs showed that there was no

(31) C. A. Brown and H. C. Brown, *J. Amer. Chem. Soc.*, **84**, 2829 (1962).

(32) A commercial model was obtained from Delmar Scientific Laboratories, Inc., Maywood, Ill.

detectable difference in reaction half-times in all-glass reactors or when sampling was being conducted.

Analyses.—Samples were analyzed by glpc and compared with known materials. The following liquid phases were used: adiponitrile on firebrick (1-pentene) and tetracyanoethylated pentaerythritol (TCEPA) on Chromosorb P (4-vinylcyclohexene, 2-methyl-1,5-hexadiene).

Registry No.—Sodium borohydride, 16940-66-2; nickel(II) acetate, 373-02-4; safrole, 14871-41-1; 1-octene, 111-66-0; cyclopentene, 142-29-0; cyclohexene, 110-83-8; cyclooctene, 931-88-4.

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Diastereomers of Quinic Acid. Chemical and Nuclear Magnetic Resonance Studies

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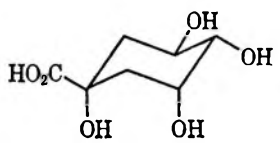
(±), (−), and (+)-*epi*-Quinides (γ-lactones of 34/15 and 45/13-tetrahydroxycyclohexanecarboxylic acids) have been prepared from their respective acetates. (+)-*epi*-Quinide triacetate separated by a spontaneous resolution in the crystallization of the optically impure (±) compound. *scyllo*-Quinic acid [*meso*-(4/135)-tetrahydroxycyclohexanecarboxylic acid] was also prepared from its acetate and its structure and conformation were determined. The 3.0- and 6.5-Hz splittings of the H-4 proton resonance in the 100-MHz nmr spectrum of the *epi*-quinic anion can most reasonably be assigned to *gauche* and *trans* splittings of a deformed chair (**9**), indicating that the H-4 and either H-3 or H-5 are axial. The magnitude of the *trans* coupling is considerably lower than that observed for other isomers. Ir and nmr (both ordinary and decoupled) spectra of *epi*-quinide triacetate verify a γ-lactone structure with the hydroxyls on C-4 and C-5 equatorial (**11**). Of particular interest in the nmr spectrum are the zero value of $J_{2(a),3(e)}$, the 1.0-Hz value for $J_{3(e),4(a)}$, and the 3.5-Hz long-range coupling between the equatorial methylene protons. The 9.0-Hz triplet splitting in H-4 in the nmr spectrum of *scyllo*-quinic acid clearly indicates that the three hydroxyls are equatorial (**13** or **14**). The formation of δ-lactone **16** on prolonged heating in acetic acid establishes that the carboxyl is *cis* to the 4-hydroxyl group and that *scyllo*-quinic acid has structure **14**.

(−)-Quinic acid, intimately involved in the "shikimic acid route" of the main pathway of aromatic biosynthesis, is one of eight diastereoisomeric 1,3,4,5-tetrahydroxycyclohexanecarboxylic acids. Of the eight such acids, only two, (−)-quinic acid (**1**) and its mirror image (**2**), (+)-quinic acid, are known.[1a] Gorin[2] isomerized (−)-quinic acid with acetic acid–sulfuric acid mixtures and obtained, after acetylation, three acetates. These were assigned the structure (−)-*epi*-



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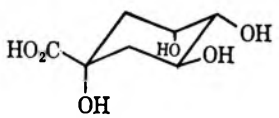

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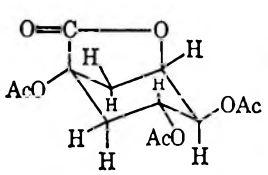
quinide triacetate (**3**), (±)-*epi*-quinide triacetate, and *scyllo*-quinic acid tetraacetate, derived from one of the four *meso* acids. The structural assignments were based on the positions of the acetoxy protons in their respective nmr spectra and a series of reactions of the carboxyl-reduced derivatives, quinicols. Gorin favored **4** [*meso*-(35/14)-tetraacetoxycyclohexane-1-carboxylic acid] over **5** [the (4/135) isomer] for the structure of *scyllo*-quinic acid tetraacetate, mainly on the basis of extrapolated kinetic data. Since *epi*-quinic acid is the only isomer (pair) other than quinic acid which may be optically active, the structural recognition of *epi*-quinide triacetate was on a sound basis (although two of the *meso* acids can form optically active lactones).



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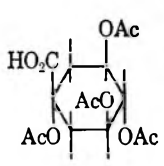

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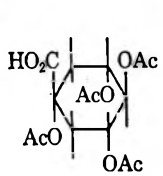

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The nomenclature of the quinic acids is in a state of uncertainty. The "Tentative Rules for Cyclitol Nomenclature" proposes that the quinic acids be named according to cyclitol rules. In our opinion such an action would be premature without radical changes being made to avoid grave errors. In this paper the system currently in general use will be followed: the carboxyl will be numbered 1 and will be drawn above the ring; the numbering will be clockwise as in the Maquenne system.[1b] Thus (−)-quinic acid is (−)-(3/145)-tetrahydroxycyclohexane-1-carboxylic acid, and (+)-quinic acid is the (+)-(5/134) isomer. We realize that it is not immediately apparent that these two are enantiomers, but to give them the same Maquenne fraction requires both clockwise and counterclockwise numbering. This leads to a remarkable confusion in describing the reactions discussed in this paper and in relating the acids of aromatic biosynthesis from 5-dehydroquinic acid. The comparable confusion possible in the carbohydrates and inositols has been sidestepped by using trivial names *solely* as a basis of nomenclature. Hence the trivial names (±)-*epi*-quinic and *scyllo*-quinic acids introduced by Gorin will be retained because of their convenience. The Sequence Rule[3,4] nomenclature, although awkward in use, is a definitive nomenclature: (−)-quinic acid is (1*R*:3*R*:4*S*:5*R*)-3/145-tetrahydroxycyclohexane-3-car-

(1) (a) T. Posternak, "The Cyclitols," Holden-Day, Inc., San Francisco, Calif., 1965, p 268 ff; (b) p 8 ff.

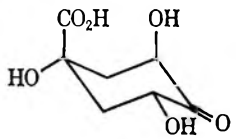
(2) P. A. J. Gorin, *Can. J. Chem.*, **41**, 2417 (1963).

(3) R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964).

(4) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

boxylic acid and (−)-*epi*-quinic acid is probably (1*R*:3*R*:4*S*:5*R*)-3,4/1,5-tetrahydroxycyclohexane-1-carboxylic acid (and not its mirror image).

A possible synthesis of *epi*-quinic acid would be by the reduction of 4-dehydroquinic acid (**6**). Haslam and Marriott[5] recently reported this reduction to give (−)-quinic acid and not *epi*-quinic acid under neutral conditions. It would be necessary to effect a conformational change in the 4-dehydroquinic acid to have any success with this approach, since carbonyl reduction usually produces an axial hydroxyl group. Such a conformational change does not appear feasible at the present time.



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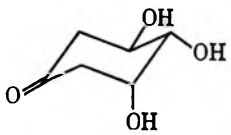

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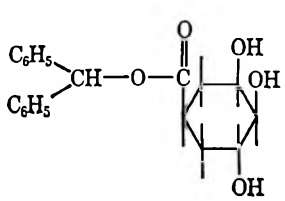
A second possible synthesis of *epi*-quinic acid would be the cyanohydrin reaction with a derivative of (3/45)-trihydroxycyclohexanone (**7**). (3/45)-Triacetoxycyclohexanone reacts to give only (−)-quinic acid.[6] We have used this reaction and the cyanohydrin reaction with the 4,5-isopropylidene derivative of (**7**) to prepare ^{14}COOH-labeled quinic acid.

Repetition of Gorin's isomerization and acetylation procedure led to a mixture of acetates which was fractionally crystallized as described, and the same three products were isolated: (−)-*epi*-quinide triacetate, mp 216–220°, $[\alpha]^{26}$D −120° (lit. mp 209–210°, $[\alpha]^{25}$D −119°);[2] (±)-*epi*-quinide triacetate, mp 186–188° (lit. mp 182–183°); and *scyllo*-quinic acid tetraacetate, mp 203–205° (lit. mp 198–200°). Spontaneous crystallization of (+)-*epi*-quinide triacetate occurred during a fractionation of racemic *epi*-quinide triacetate with chloroform, and it was possible to prepare it by seeding reasonable quantities of the (+) enantiomer, $[\alpha]^{27}$D +120°, from the racemic form.

Saponification of either (−)- or (±)-*epi*-quinide triacetate by sodium hydroxide and removal of the sodium ions with a cation-exchange resin gave the corresponding *epi*-quinide on evaporation *in vacuo*. When *epi*-quinide was saponified with sodium hydroxide and again freed of sodium ions by passage through a cation-exchange resin column at 1°, the resulting solution reacted smoothly with diphenyldiazomethane to form the benzhydryl ester **8**. If the solutions of free



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epi-quinic acid were lyophilized at 0.01 mm, with a final overnight drying at room temperature, a mixture of lactone and acid was always formed. Pure *epi*-quinide could be readily obtained by trituration of the semicrystalline solid with absolute alcohol. This ease of lactonization of *epi*-quinic acid, compared with that

(5) E. Haslam and J. E. Marriott, *J. Chem. Soc.*, 5755 (1965).
(6) R. Grewe and E. Vangermain, *Chem. Ber.*, **98**, 104 (1965).

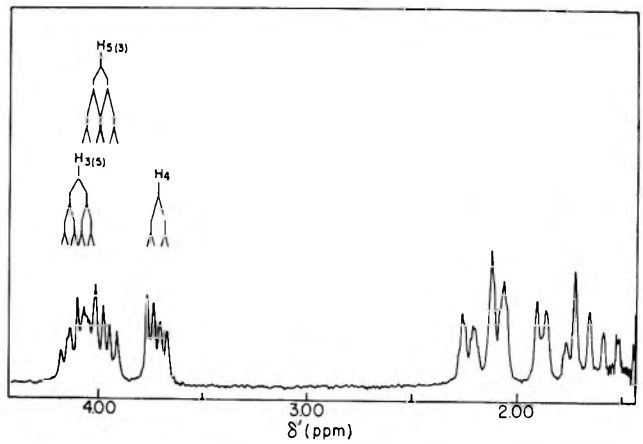
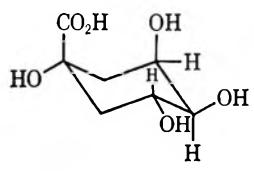


Figure 1.—100-MHz nmr spectrum of (−)-*epi*-quinic acid anion in 1 *N* NaOD in D_2O at 31°.

of quinic acid or *scyllo*-quinic acid, was completely unexpected. Quinic acid forms acetone quinide on treatment with acetone and a mineral acid.[7] Thermal lactonization of quinic acid is carried out by heating at 230° for a short time (yield not given).[8] Longer heating times cause racemization. 4-Dehydroquinic acid is reported to form the lactone diacetate on treatment with acetic anhydride.[5] 5-Dehydroquinic acid aromatizes under these conditions to form 4,5-diacetylprotocatechuic acid.[5] Lactone(s) of *scyllo*-quinic acid have not been prepared prior to this work, and its lactone acetates have not been isolated from the quinic acid isomerization process used here.

The 100-MHz nmr spectrum of (−)-*epi*-quinic acid anion in 1 *N* NaOD referenced to DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) is shown in Figure 1. The spectrum is very similar to that of quinic acid in D_2O.[9] The protons on C-3, C-4, and C-5 give rise to the low-field multiplets at δ' 3.72 and 4.04, while the four methylene protons are responsible for the complex group of overlapping multiplets in the vicinity δ' 2. The δ 3.72 doublet-split doublet can be unambiguously assigned to H-4 because of the absence of a third coupling. Its two splittings of 3.0 and 6.5 Hz can be reasonably assigned to gauche and *trans* couplings, respectively. Thus H-4 would be axial together with either H-3 or H-5, indicating that *epi*-quinic acid has the conformation (a)-CO_2H (**9**) and not the (*e*)-CO_2H (**10**). Unfortunately, because of the low magnitude of



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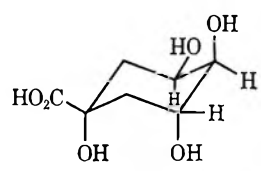

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the *trans* coupling there is some doubt about this assignment. For example, in quinic acid[9] and *scyllo*-quinic acid (*vide infra*), the 3–4 and/or 4–5 *trans* couplings are 9.0 Hz.

The overlapping multiplets for H-3 and H-5 cannot be adequately resolved by first-order methods. The

(7) H. O. L. Fischer, *Ber. Deut. Chem. Ges.*, **54**, 775 (1921).
(8) J. Wolinsky, R. Novak, and R. Vasileff, *J. Org. Chem.*, **29**, 3596 (1964).
(9) J. Corse, R. E. Lundin, E. Sondheimer, and A. C. Waiss, Jr., *Phytochemistry*, **5**, 767 (1966).

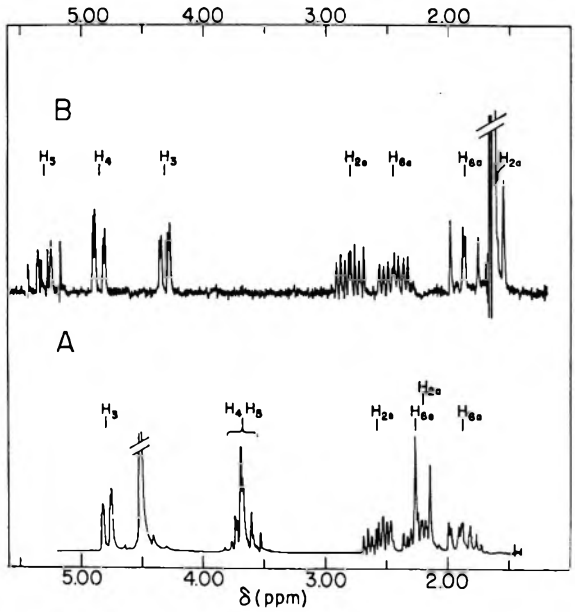


Figure 2.—(a) 100-MHz nmr spectrum of (−)-*epi*-quinide in D_2O at 60°; (b) 100-MHz nmr spectrum of (−)-*epi*-quinide triacetate in benzene-d_6 at 75°.

present data are insufficient for a computer analysis that would provide accurate values for the couplings of the four methylene protons with H-3 and H-5. Hence the splitting scheme in Figure 1 should be taken with some reservation. However, these values are at least partially confirmed by a first-order analysis of the 220-MHz spectrum of the anion. A value of 8 Hz for $J_{2(a),3(e)}$ is entirely too high for a *gauche* coupling. The alternate conformation, (e)-CO_2H, provides a more reasonable fit, as shown in Table I, but it must be

TABLE I

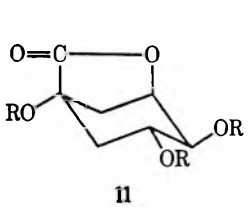
SPIN–SPIN COUPLING CONSTANTS OF *epi*-QUINIC ACID IN 1 *N* NaOD[a]

Interaction	Coupling constant,
$J_{2(e),3(a)}$	~5
$J_{2(a),3(a)}$	~8
$J_{3(a),4(e)}$	3.0
$J_{4(e),5(e)}$	6.5
$J_{5(e),6(e)}$	~4
$J_{5(e),6(a)}$	~6

[a] Based on conformation **10** with (e)-CO_2H.

emphasized that a first-order analysis is not fully justified. The coupling constants observed could result from a deformed or interconverting chair conformation. The low $\Delta G°$ of these conformations (*cf.* Table II) is indicative of the latter possibility.

The structures of *epi*-quinide and its triacetate could reasonably be either γ- or δ-lactones (**11** or **12**), respectively. Gorin reported *epi*-quinide triacetate to have a



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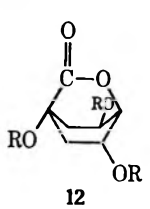

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carbonyl stretching frequency at 1795 cm^{-1}, which clearly indicates a γ-lactone.[10] (±)-*epi*-Quinide itself

TABLE II

PREDICTED CONFORMATIONAL PREFERENCES OF ISOMERIC QUINIC ACIDS FROM ENERGY TABLES[a]

Acid	Hydroxyl group configurations	Conformation[b] (e)-CO_2H	Conformation[b] (a)-CO_2H
(±)-Quinic	3/145, 5/134	1.74*	3.09
(±)-*epi*-Quinic	34/15, 45/13	2.61	2.22*
scyllo-Quinic (**14**)	*meso*-(4/135)	3.48	1.35*
Unknown *meso* (**13**)	*meso*-(35/14)	0.87*	3.96
Unknown *meso*	*meso*-(345/1)	1.74*	3.09
Unknown *meso*	*meso*-(0/1345)	2.61	2.22*
4-Dehydroquinic		1.74[c]	2.22
5-Dehydroquinic		0.87*[c]	2.09

[a] Values in kcal/mol ($-\Delta G°$) from D. L. Robinson and D. W. Theobald, *Quart. Rev.* (London), **21**, 314 (1967). [b] Preferred conformation is asterisked; values for hydroxyl groups are those in hydroxylic solvents. [c] See text.

shows a strong absorption at 1788 cm^{-1}, while our triacetate shows one at 1790 cm^{-1} in close agreement with Gorin's value. The lactone absorptions match bands in the quinic acid series [(−)-quinide, 1796 cm^{-1}; (−)-quinide triacetate, 1800 cm^{-1}] and leave no doubt of the γ-lactone structure **11** (R = H).

The 100-MHz nmr spectrum of (±)-*epi*-quinide in D_2O (referenced to DSS) is shown in Figure 2a. The resonances of the protons on carbons 3, 4, and 5 fall between δ′ 3.5 and 4.5, while the methylene protons on carbons 2 and 6 give rise to the bands at δ′ 1.7–2.7. The singlet at δ′ 4.50 is due to residual HDO. Because it was impossible to analyze the overlapping multiplets from two of the protons in the vicinity of δ′ 3.7 (these were subsequently assigned to H-4 and H-5 as shown on the basis of the triacetate assignment), the triacetate of *epi*-quinide **11** (R = Ac) was run in both chloroform-*d* and benzene-d_6. Its spectrum in the latter solvent is shown in Figure 2b. The differential shifts of the carbinol and axial methylene protons in this solvent make possible a straightforward analysis of the entire spectrum. The multiplet assignments are shown on the figure, and the apparent coupling constants based on a first-order analysis of the splitting patterns are given in Table III. It is obvious that the triacetate must have

TABLE III

COUPLING CONSTANTS[a] FOR SOME SUBSTITUTED QUINIDES

Coupling constant	(−)-*epi*-Quinide triacetate $CDCl_3$	(−)-*epi*-Quinide triacetate C_6D_6	(±)-*epi*-Quinide tribenzoate C_6D_6	(−)-Quinide tribenzoate C_6D_6
$J_{2(e),6(e)}$	3.5	3.6	3.6	2.0
$J_{2(e),2(a)}$	11.8	11.8	11.8	12
$J_{6(e),6(a)}$	12.0	11.9	11.9	
$J_{2(e),3(e)}$	7.0	6.8	6.8	5.2
$J_{2(a),3(e)}$	0.0	0.0	0.0	~0
$J_{3(e),4(e)}$				4.7–5.2
$J_{3(e),4(a)}$	1.0	1.2	1.2	
$J_{4(e),5(a)}$				4.7
$J_{4(a),5(a)}$	8.5	8.5	8.5	
$J_{5(a),6(e)}$	7.0	7.4	7.4	8.0
$J_{5(a),6(a)}$	10.1	10.8	10.8	10.4

[a] In hertz.

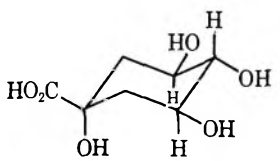
the γ-lactone structure **11** (R = Ac), in agreement with the ir data. Spin decoupling was used to identify H-4 both in benzene-d_6 and for the more complex spectrum obtained in chloroform-*d*, since it is the only HOCH

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1959, p 178.

proton *not* coupled to a methylene proton. Table III also gives the coupling constants obtained from a similar analysis of the spectra of the tribenzoates of *epi*-quinide and quinide, which was used as a model structure for checking the assignment of couplings. Because the multiplets from H-2 and H-6 overlap in the quinide tribenzoate spectrum, the values of the couplings to them are only approximate. Otherwise, the agreement in the values of the corresponding constants is most satisfactory.

Three couplings deserve special comment: the essentially zero coupling of the 2-axial proton with the 3-equatorial, the small coupling of this proton (H-3(e)) to the 4-axial, and the long-range coupling between the 2- and 6-equatorial protons. Dunkelblum and Klein[11] recently reported that the couplings of the equatorial proton on C-3 to vicinal axial protons were immeasurably small in 1–3 lactone-bridged cyclohexanes. They explain this result on the basis of a dihedral angle (roughly 90°) for these two couplings in the bridged-ring structure which approximates the zero coupling angle in the Karplus equation.[12] The small coupling observed in this study for $J_{3(e),4(a)}$ may result from the hydroxyl substituent on C-4. However, from the 60-MHz spectra reproduced in the earlier study[11] it is questionable whether a 1-Hz splitting would have been resolved. The rather large long-range coupling between the equatorial methylene protons is probably a consequence of the distorted chair conformation of the bridged γ-lactone cyclohexane structure.

The 100-MHz nmr spectrum of *scyllo*-quinic acid in 1 *N* NaOD (referenced to DSS) is shown in Figure 3. Again, the proton resonances on carbons bearing hydroxyl groups in the vicinity of δ′ 3.5 are shifted *ca.* 1.5 ppm downfield from the methylene protons whose multiplets at *ca.* δ′ 2.0 are so completely overlapped that no analysis of these resonances was attempted. The triplet centered at δ′ 3.28 can be immediately assigned to H-4 because of the absence of any indication of coupling to more than two protons. The 9.0-Hz splitting is consistent with either the *meso*-(35/14) structure in the (e)-CO_2H conformation **13**, or the *meso*-(4/135) structure in the (a)-CO_2H conformation



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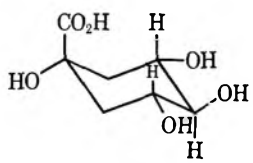

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14, wherein H-3, H-4, and H-5 are *all axial*, and it is not possible from the nmr spectrum to distinguish between the two possibilities. The complex multiplet centered at δ′ 3.68 cannot be satisfactorily analyzed by first-order methods, and again the splittings shown on Figure 3 must be viewed with reservation. Table IV lists the approximate couplings, which are completely compatible with the two possible structures.

The large *gauche* couplings of the 2- and 6-equatorial protons to the 3- and 5-axial protons again confirm the finding of Williams and Bhacca[13] that an equatorial

(11) E. Dunkelblum and J. Klein, *Tetrahedron Lett.*, 55 (1968).
(12) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(13) D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, **86**, 2742 (1964).

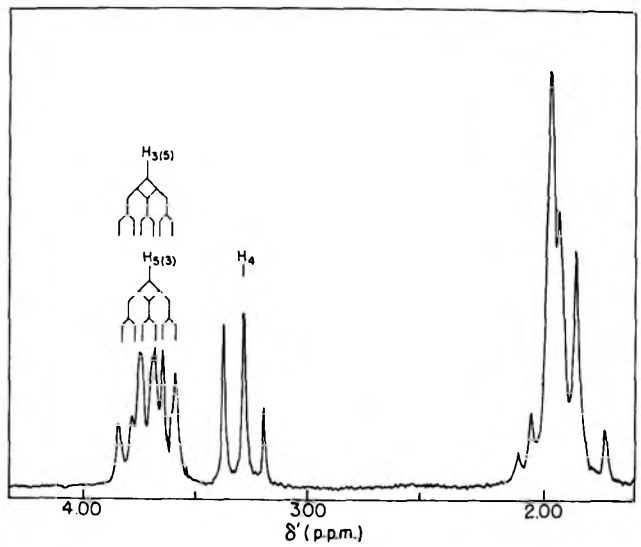


Figure 3.—100-MHz nmr spectrum of *scyllo*-quinic acid anion in 1 *N* NaOD in D_2O at 31°.

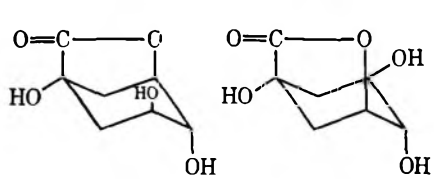
TABLE IV
SPIN–SPIN COUPLINGS IN *scyllo*-QUINIC ACID[a]

Interaction	Coupling constant, Hz
$J_{2(a),3(a)}$	~9
$J_{2(e),3(a)}$	~6
$J_{3(a),4(a)}$	9.0
$J_{4(a),5(a)}$	9.0
$J_{5(a),6(e)}$	~6
$J_{5(a),6(a)}$	~8

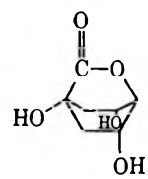
[a] In 1 *N* NaOD.

oxygen substituent apparently causes a *gauche* coupling to be unexpectedly large (4.5 ± 1 Hz), whereas with an axial substituent the coupling falls within the usual range (2.5–3.2 Hz). In an earlier paper[9] this dependence of *gauche* coupling on oxygen conformation was applied to a discussion of quinic acid and some of its derivatives.

Although nmr spectroscopy cannot distinguish between the *meso*-(35/14) (**13**) and *meso*-(4/135) (**14**) structures for *scyllo*-quinic acid, the position of the lactone carbonyl absorption band in the infrared spectrum of the corresponding lactone should clearly delineate the structure, similar to *epi*-quinide (*vide supra*). Structure (**13**) could be expected to form a racemic pair of γ-lactone isomers (**15**), and structure **14** would form a *meso* δ-lactone (**16**). On prolonged



15

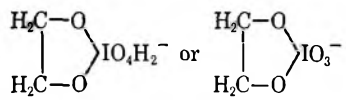


16

heating of an acetic acid suspension of *scyllo*-quinic acid, solution was effected with lactonization. The lactone showed a strong infrared absorption band at 1720 cm^{-1}, as is expected of **16**. This clearly indicates that the 4-hydroxy and the carboxy groups are *cis* to each other. It then follows that *scyllo*-quinic acid has configuration **14**, *meso*-(4/135)-tetrahydroxycyclohexane-1-carboxylic acid. The 100-MHz nmr spectrum of *scyllo*-quinide gave an overlapping group of multiplets

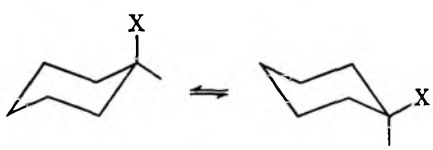
which could not be resolved. No increase in resolution occurred in acetylating or benzoylating the free hydroxy groups. The nmr spectrum did not resemble those of the several γ-lactones of the quinic and *epi*-quinic acid series.

At the suggestion of one of the referees, the reaction of *scyllo*-quinide with periodate was explored. Although the periodate oxidation method is of general application, the requirement of the formation of a cyclic periodate ester as the decomposing entity[14] could severely limit the use of this reaction in the rigid bicyclic quinic



acid series. This proved to be the case. (−)-Quinide and *cis*- and *trans*-1,2-cyclohexanediols reacted quickly with sodium metaperiodate solutions under the conditions of Aspinall and Ferrier.[15] However, no loss of periodate could be detected after 4 hr with (−)-*epi*-quinide nor after 65 hr with *scyllo*-quinide. The vicinal hydroxyl groups in *epi*-quinide are *trans* as they are in **15**, and the rigidity of these lactones prevents the five-membered periodate ring from forming.

The conformations of *scyllo*-quinic and *epi*-quinic acids in solution, wherein the carboxyl groups are axial, differ from quinic acid and all of its derivatives, which have the carboxyl group equatorial (except for the pertrimethylsilyl derivative of quinic acid).[16] These conformational preferences are in agreement with the predictions based on the standard free energy change ($-\Delta G_x^\circ$) for the equilibrium[17,18] shown. The



values for the eight stereoisomeric quinic acids are summarized in Table II. The high difference in energies for the two conformers in *scyllo*-quinic acid may account in part for the difficulty in lactonization, since the groups on adjoining carbon atoms must eclipse each other in conformational changes. This may be made clear in a study of the 35/14 acid **13**, which, although it has two hydroxyls capable of forming lactones, has an even greater free-energy difference between the two conformers than *scyllo*-quinic acid.

The more nearly equal energies of the two conformers of *epi*-quinic acid may similarly account for the apparent deformed-chair conformation observed. The predictions of conformation preference for quinic acid and 5-dehydroquinic acid agree with observation.[9,16] However, the prediction for 4-dehydroquinic acid is at variance with the conformation suggested by Haslam and Marriott[5] on the basis of hydrogenation results. It should be noted that the values of $-\Delta G^\circ$ have been derived from measurements on chair forms of cyclohexanes. The twist conformations frequently favored by cyclohexanones[19] may require $-\Delta G^\circ$ values sufficiently different from the chair values to render use of the latter questionable.

The epimerization of the hydroxyl groups of quinic acid parallels those of tetra- and pentahydroxy cyclohexanes rather than those of the inositols. The methylene groups, as shown by Angyal, Gorin, and Pitman,[20] markedly affect the course of the reactions. The formation of (−)-*epi*-quinic acid may involve changes only in the 4-hydroxyl group, favorably flanked as it is by *cis* and *trans* adjacent hydroxyl (or acetoxy) groups. However, the formation of large amounts of (+)-*epi*-quinic acid and *scyllo*-quinic acids clearly results from displacements on the 3 and 5 carbon atoms.

Experimental Section

The melting points were taken on a Kofler hot stage and are corrected. Other physical measurements were made on the following instruments: nmr spectra, internally locked Varian HR-100;[21] infrared spectra, Cary Model 90; optical rotations, Bendix polarimeter type 143A; ORD, Cary Model 60; uv spectra Cary Model 15. The nmr spectra were run at concentrations of *ca.* 5% under the conditions noted with *t*-butyl alcohol-*d* as internal lock for aqueous solutions. The position of the lock resonance in respect to internal DSS was determined in a subsequent scan of the solvent at the same temperature.

Isomerization of Quinic Acid.[2]—A solution of 10 g of (−)-quinic acid in 500 ml of acetic acid to which 7.5 ml of sulfuric acid had been added was heated under reflux for 100 hr. The solution was then cooled, acetylated, and worked up as described. The fractionation of the mixed acetates proceeded by a series of recrystallizations from $CHCl_3$–ethyl acetate.

(−)-*epi*-Quinide Triacetate (3).—This compound was less soluble in $CHCl_3$ than the (±) modification or *scyllo*-quinic acid tetraacetate: yield 2.35 g; mp 216–220°; $[\alpha]^{24}D$ −120°, −118° (*c* 0.5, $CHCl_3$) (lit.[2] mp 209–210°, $[\alpha]^{24}D$ −119°).

Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 52.0; H, 5.27.

(±)-*epi*-Quinide Triacetate.—This compound was recrystallized from ethyl acetate–$CHCl_3$–ether: yield 0.79 g; mp 186–188°; $[\alpha]^{24}D$ 0° (*c* 1, $CHCl_3$); ir carbonyl stretching 1790, 1838, and 1752 cm^{-1} (KBr pellet) [lit.[2] mp 182–183°; ir carbonyl stretching on mixture of (−) and (±) acetates 1795 and 1750 cm^{-1}]. The 100-MHz nmr and ir spectra of the (±) isomer and (−) isomers were superimposable.

Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 52.1; H, 5.34.

(+)-*epi*-Quinide Triacetate.—A sample of 17.6 g of *epi*-quinide triacetate, $[\alpha]^{26}D$ −19°, was dissolved in the minimum amount of boiling $CHCl_3$ and the solution was placed in the refrigerator. After standing for 2 days, 4.2 g of crystals (dry weight) had separated and were collected, $[\alpha]^{25}D$ +92°. These were again recrystallized from $CHCl_3$: yield 0.92 g; mp 216°; $[\alpha]^{27}D$ +120° (*c* 0.5, $CHCl_3$). The 100-MHz nmr spectrum was superimposable on the spectra of the (−) enantiomer or the (±) compound.

Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 52.1; H, 5.41.

***scyllo*-Quinic Acid Tetraacetate (4).**—This acid was purified by treating crude lactone fractions [containing (±)-*epi*-quinide triacetate] with dilute $KHCO_3$ solution, filtering, and carefully acidifying the filtrate recrystallized from ether–petroleum ether: yield 3.50 g; mp 203–205° (lit.[2] mp 198–200°); $[\alpha]^{24}D$ 0° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{15}H_{20}O_{10}$: C, 50.00; H, 5.60. Found: C, 50.1; H, 5.53.

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(15) G. O. Aspinall and R. J. Ferrier, *Chem. Ind.* (London), 1216 (1957).

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(18) J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, p 199.

(19) D. L. Robinson and D. W. Theobald, *Quart. Rev.* (London), **21**, 314 (1967).

(20) S. J. Angyal, P. A. J. Gorin, and M. E. Pitman, *J. Chem. Soc.*, 1807 (1965).

(21) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

scyllo-**Quinic Acid (14).**—A solution of 1 g of *scyllo*-quinic acid tetraacetate (4) in 13 ml of 2 *N* NaOH was allowed to stand for 4 hr at room temperature. The reaction mixture was freed of sodium ions by passing through a Dowex AG-50W-X2, 100–200 mesh, acid-form column (12 mm × 40 cm) and eluting with water until the eluate was neutral. The eluate was evaporated to dryness *in vacuo* and the crystalline acid was recrystallized from acetone–petroleum ether, yield 0.47 g mp 228–230°.

Anal. Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.29. Found: C, 43.6; H, 6.25.

scyllo-**Quinide.**—A suspension of 0.5 g of *scyllo*-quinic acid in 15 ml of acetic acid was heated on a steam bath for 1 week with occasional shaking. The resulting solution was filtered and the filtrate was evaporated to dryness in a N_2 stream. The product, a hygroscopic glass, was dried at 100° (0.2 mm). A Nujol mull showed a carbonyl absorption band at 1720 cm^{-1}.

Anal. Calcd for $C_7H_{10}O_5$: C, 48.27; H, 5.79. Found: C, 48.3; H, 5.92.

Saponification of a sample of *scyllo*-quinide and recovery of the free acid in a manner similar to the hydrolysis of the tetraacetate gave an essentially quantitative recovery of acid.

Equal volumes of 0.03 *M* sodium *m*-periodate and 0.015 *M* *scyllo*-quinide were mixed at room temperature. Aliquots of 1 ml were taken at intervals and diluted to 250 ml, and the absorbance of the diluted solution was measured at 223 mμ.[15] There was no observable reduction of periodate over a period of 65 hr. Under the same conditions, (−)-quinide reacted with 1 mol of periodate in 10 min and *cis*- and *trans*-1,2-cyclohexanediols each reacted with 1 mol of periodate in less than 2 min. (−)-*epi*-Quinide showed no reaction in 4 hr.

Benzhydryl *scyllo*-**Quinate.**—A solution of 1 g of *scyllo*-quinic acid in 25 ml of ethyl acetate was treated with diphenyldiazomethane until the pink color just persisted. The solvent was removed *in vacuo*, and the residue was washed with petroleum ether and then recrystallized from ethyl acetate–petroleum ether, mp 84–87°.

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.0; H, 6.23.

(±)-*epi*-**Quinide.**—A solution of 1 g of (±)-*epi*-quinide triacetate in 13 ml of 2 *N* NaOH was allowed to stand overnight at room temperature. The sodium ions were removed by passing the saponified ester through a Dowex AG-50X2 column (12 mm × 40 cm) and eluting with water until all the acids were off the column. The eluate was evaporated to dryness *in vacuo* and the last traces of acetic acid were blown off in a N_2 stream. The semisolid material was triturated with absolute EtOH and chilled. The resulting crystals were collected and recrystallized from EtOH, yield 0.3 g, mp 202–204°.

Anal. Calcd for $C_7H_{10}O_5$: C, 48.27; H, 5.79. Found: C, 48.5; H, 5.80.

Benzhydryl (±)-*epi*-**Quinate.**—A solution of 1 g of (±)-*epi*-quinide, after standing for 1 hr in 10 ml of *N* NaOH at room temperature, was passed through a Dowex AG-50X2 column as before. The eluate was concentrated to about 5 ml by evaporation at 35° *in vacuo* and treated with a slight excess of diphenyldiazomethane. The reaction product was evaporated to dryness washed with petroleum ether, and recrystallized from ethyl acetate–petroleum ether, mp 122–124°. The product was analyzed after drying at 100° *in vacuo*.

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 66.5; H, 6.13.

The product was also analyzed after drying at room temperature.

Anal. Calcd for $C_{20}H_{22}O_6 \cdot H_2O$: C, 63.82; H, 6.43. Found: C, 63.5; H, 6.25.

(−)-*epi*-**Quinide.**—A solution of 1 g of (−)-*epi*-quinide triacetate was saponified and worked up exactly as described for (±)-*epi*-quinide, mp 196–197°, $[\alpha]_D^{23}$ −127° (*c* 0.5, H_2O). The rotation of (−)-*epi*-quinide, $[\alpha]_D^{23}$ −127°, shows a negative Δ value in relation to (−)-*epi*-quinic acid, in accord with Klyne's modification[22] of Hudson's lactone rule.

Anal. Calcd for $C_7H_{10}O_5$: C, 48.27; H, 5.79. Found: C, 48.4; H, 5.75.

In an attempt to prepare free (−)-*epi*-quinic acid, the saponification mixture was cooled to 0° and the ion-exchange column was used in a cold room at 1°. The eluates were frozen and lyophilized at 0.005 mm. As soon as the ice film on the outside of the lyophilization flask melted, the flask was removed from the lyophilization apparatus and placed in a vacuum desiccator over P_2O_5 and it was evacuated to 0.01 mm. The sample of *epi*-quinic acid was analyzed the next morning.

Anal. Calcd for $C_7H_{12}O_6$ (acid): C, 43.75; H, 6.29. Found: C, 45.0; H, 6.15. Calcd for $C_7H_{10}O_6$ (lactone): C, 48.27; H, 5.79.

The optical rotation of (−)-*epi*-quinic acid was taken by dissolving (−)-*epi*-quinide in sodium hydroxide, $[\alpha]^{24}D$ −22° (*c* 1). The nmr spectrum was taken by dissolving *epi*-quinide in D_2O and adding an excess of NaOD.

The ORD of (−)-*epi*-quinic acid shows a strong negative Cotton effect, in contrast to (−)-quinic acid, which gave a low-wavelength positive Cotton effect.

Benzhydryl (−)-*epi*-**Quinate.**—This substance was prepared from (−)-*epi*-quinide in the same manner as the (±) isomer, mp 127–128°, $[\alpha]^{24}D$ −34°. The elementary analyses were very dependent on drying conditions. Drying *in vacuo* over P_2O_5 at room temperature gave the hemihydrate.

Anal. Calcd for $C_{20}H_{22}O_6 \cdot {}^1/_2H_2O$: C, 65.38; H, 6.31. Found: C, 65.6; H, 6.25.

This water of crystallization was apparent in the nmr spectrum (run in dimethyl sulfoxide-d_6). Drying overnight at 80° *in vacuo* caused the crystalline sample to become a gum; water elimination in the ring evidently occurred. This phenomenon did not take place with the other benzhydryl esters described here.

Anal. Found: C, 69.0; H, 5.97.

Benzhydryl (−)-**Quinate.**—A suspension of 2 g of (−)-quinic acid in 25 ml of ethyl acetate was warmed and treated with diphenyldiazomethane until reaction ceased. Addition of petroleum ether caused the separation of the crystalline ester in near quantitative yield. It was recrystallized from ethyl acetate–petroleum ether, mp 85–87°, $[\alpha]D$ −21° (*c* 1, EtOH).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.0; H, 6.16.

(±)-*epi*-**Quinide Tribenzoate.**—A solution of 0.28 g of (±)-*epi*-quinide in 3 ml of pyridine was warmed on the steam bath with 0.65 ml of benzoyl chloride for 0.5 hr and allowed to stand at room temperature for 2 hr. The reaction mixture was stirred with 50 ml of ethyl acetate and 200 ml of water. After separation, the ethyl acetate layer was successively washed with cold, dilute HCl, cold dilute NaOH, and cold water. After drying ($MgSO_4$), the solution was concentrated by warming in a N_2 stream. Addition of light petroleum and chilling yielded 0.53 g of tribenzoate, mp 183–184°.

Anal. Calcd for $C_{28}H_{22}O_8$: C, 69.13; H, 4.56. Found: C, 69.1; H, 4.55.

(−)-**Quinide Tribenzoate.**—This compound was prepared from quinide analogously to the *epi* isomer in near quantitative yield, mp 154–155° (lit. mp 148°).[23]

Anal. Calcd for $C_{28}H_{22}O_8$: C, 69.13; H, 4.56. Found: C, 69.3; H, 4.59.

Registry No.—(±)-*epi*-Quinide triacetate, 23804-26-4; (+)-*epi*-quinide triacetate, 23804-27-5; *scyllo*-quinic acid tetraacetate, 23804-28-6; benzhydryl *scyllo*-quinate, 23804-30-0; (±)-*epi*-quinide, 23804-31-1; benzylhydryl (±)-*epi*-quinate, 23804-32-2; (−)-*epi*-quinide, 23804-33-3; (−)-*epi*-quinic acid, 23804-34-4; benzhydryl (−)-quinate, 23804-35-5; (±)-*epi*-quinide tribenzoate, 23804-36-6; benzhydryl (−)-*epi*-quinate, 23804-37-7; *epi*-quinic acid, 23804-38-8; (−)-quinide tribenzoate, 23804-39-9; (±)-quinic acid, 23804-40-2; (±)-*epi*-quinic acid, 23804-41-3; 4-dehydroquinic acid, 18543-47-0; 5-dehydroquinic acid, 10236-66-5; **3**, 23804-25-3; **13**, 23804-44-6; **14**, 23804-29-7.

Acknowledgment.—We wish to thank D. C. Patterson for technical help, Dr. J. R. Scherer and Dr. W. Gaffield for the ir and ORD data, and L. White and Miss G. Secor for elemental analyses.

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The Synthesis of 6-Deoxy Homologs of Muramic Acid

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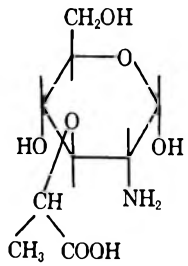
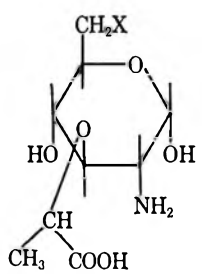
2-Amino-2,6-dideoxy-3-*O*-(D-1-carboxyethyl)-D-glucopyranose and the 6-fluoro derivative have been synthesized. Fluorine was introduced *via* displacement of the corresponding tosylate with tetrabutylammonium fluoride.

Muramic acid (I), being a constituent of the cell walls of both gram-positive and gram-negative bacteria



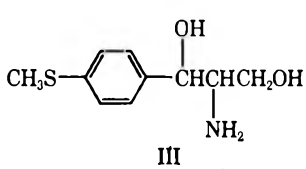
I

and vital to cell-wall synthesis, presents an interesting point of attack for the inhibition of cell-wall synthesis.[1] Lindberg[2] prepared several homologs of muramic acid with variations of the lactic acid side chain. These compounds exhibited no antibacterial activity when tested *in vitro*. Two modifications, which appeared interesting both chemically and biologically, were those which involved the replacement of the 6-hydroxyl group, shown in structure II.



IIa, X = H
b, X = F

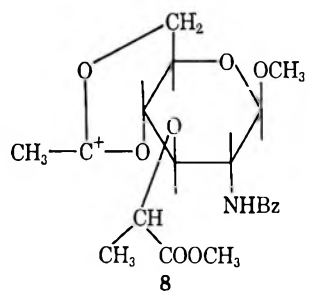
This paper describes the synthesis of (+)-6-deoxy- and 6-fluoro-6-deoxymuramic acid. The intermediate (1) was prepared according to the method of Gigg and Carrol.[3] In order to separate the requisite D isomer from the isomeric mixture, the salt of (+)-(1*R*,2*S*)-2-amino-1-[4-(methylthio)phenyl]-1,3-propanediol (III)[4] was prepared. This method of separation proved far superior to the one utilized by Gigg, which involved the separation of the S-benzylpseudothiourea salt.



III

The opening of the oxazolidine ring in **1b** with subsequent rearrangement to the glucopyranose has been performed under a variety of conditions. Since the proposed synthetic approach required the protection of the glycosidic hydroxyl group, the conditions of methanolic hydrogen chloride utilized by Lindberg[2] were chosen. In this fashion, the opening of the oxazolidine ring and introduction of the methoxy group at the 1 position could be achieved simultaneously. The product of this rearrangement was reported as the corresponding acid.[5] However, analytical as well as nmr data confirmed the structure as being the ester 2a. Tritylation of **2a** with subsequent acetylation produced **2b**, which was heated with glacial acetic acid to give **2c**.

A search of the literature indicates that no satisfactory method exists for the introduction of fluorine into a carbohydrate molecule under mild conditions. Recently, Gubitz[6] examined and successfully employed tetrabutylammonium fluoride (TBAF) for this purpose. Originally it was planned to activate the 6 position of **2c** by formation of the mesylate **2d** followed by displacement with fluoride. When **2d** was treated with tetrabutylammonium fluoride, the desired compound **3a** was not obtained; instead a mixture of **2c** and **2e** was produced, probably *via* the intermediate **8** formed by internal displacement of the mesylate.



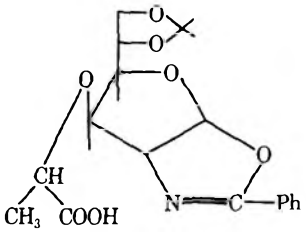
8

In view of this failure, attention was turned to the more reactive tosylate **2f**, which was readily prepared from **2a**. Treatment of **2f** with a slight excess of TBAF produced **3b** in good yield. Hydrolysis of **3b** in 3 *N* HCl gave **4** as a hygroscopic solid.

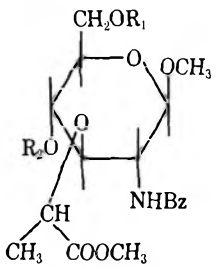
The deoxy homolog **7** was obtained from **2f** by treatment with sodium iodide in acetone, which produced the iodo lactone **5a**. This compound exhibited a molecular ion peak at *m/e* 235, and the nmr spectrum supported this structure. Further confirmation was obtained by conversion of **5a** with sodium methoxide in

(1) M. R. Salton, "The Bacterial Cell Wall," Elsevier Publishing Co., New York, N. Y., 1964.
(2) B. Lindberg and H. Agbach, *Acta Chem. Scand.*, **18**, 185 (1964).
(3) R. H. Gigg and P. M. Carrol, *Nature*, **191**, 495 (1961).
(4) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Amer. Chem. Soc.*, **74**, 5475 (1952).
(5) Lindberg reports this as the acid (see ref 2).
(6) F. W. Gubitz, to be published.

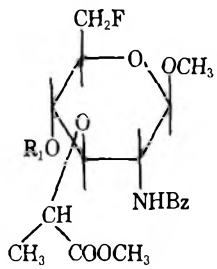
methanol into the ester **6**, whose nmr spectra exhibited six methoxy hydrogens at 165 and 170 Hz. Hydrogenation of **5a** in methanol with Raney nickel produced the 6-deoxy compound **5b**. Hydrolysis of **5b** with 3 *N* HCl produced **7** as a crystalline solid.



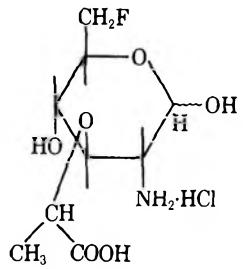
1a, (±)
b, $[\alpha]^{25}D + 66.7°$



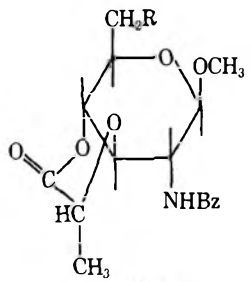
2a, $R_1 = H$; $R_2 = H$
b, $R_1 = Tr$; $R_2 = Ac$
c, $R_1 = H$; $R_2 = Ac$
d, $R_1 = Mes$; $R_2 = Ac$
e, $R_1 = Ac$; $R_2 = H$
f, $R_1 = Ts$; $R_2 = H$



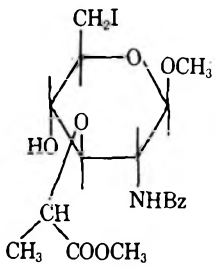
3a, $R_1 = Ac$
b, $R_1 = H$



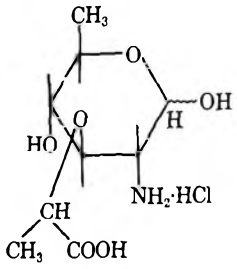
4



5a, R = I
b, R = H



6



7

Experimental Section[7]

2-Phenyl-4,5-[3-*O*-(D-1-carboxyethyl)-5,6-isopropylidene-D-glucofurano]-Δ^2-oxazoline (1b).[8]—A mixture of 94 g (0.261 mol) of the DL acid **1a** and 55 g (0.261 mol) of the amine III in 1 l. of isopropyl alcohol was heated to boiling on a hot plate. After all of the solid had dissolved, the solution was filtered and the filtrate was cooled at room temperature for 5 hr and then at 0° overnight. This cooling procedure aided crystallization of the product. The solid was collected and washed with cold isopropyl alcohol: yield 100 g; mp 165–166°.

Anal. Calcd for $C_{29}H_{37}N_2O_8S$: C, 59.20; H, 6.27; N, 4.75. Found: C, 59.07; H, 6.96; N, 4.24.

To a suspension of 60.4 g (0.105 mol) of the amine salt of **1a** in 250 ml of water and 1200 ml of ether was added dropwise 101 ml of 1 *N* HCl over a 30-min period. After the addition was complete, the ether layer was collected and dried and the ether was removed. The residual white solid **1b** was recrystallized from ethyl acetate: yield 26.5 g; mp 166–167°; $[\alpha]^{25}D$ +66.7° (*c* 1, $CHCl_3$) (lit.[8] mp 163–164°; $[\alpha]^{25}D$ +65°).

Methyl 2-Benzamido-2-deoxy-3-*O*-[D-1-(methoxycarbonyl)-ethyl]-6-*O*-trityl-β-D-glucopyranoside 4-Acetate (2b).—To a solution of 30.4 g (0.0794 mol) of **2a**[3] in 520 ml of pyridine was added 27.3 g (0.098 mol) of trityl chloride.[9] The solution was stirred at room temperature for 24 hr and then heated to 100° for 3 hr. After cooling to 0°, 41.6 ml of acetic anhydride was added. The solution was left at room temperature for 24 hr. The excess solvent and acetic anhydride were removed *in vacuo*. The residue was treated with an ice–water mixture. A gum formed which gradually solidified. The solid was removed by filtration and washed with water. The material was then suspended in 1 l. of ether and 400 ml of water, and the mixture was treated dropwise with 1 *N* HCl until the pH was 4. Methylene dichloride was then added until all of the solid had dissolved. The organic layer was collected and dried, and the solvent was removed. An oily residue was obtained, which was dissolved in hot isopropyl alcohol and chilled. An oil separated which solidified on scratching. The solid **2b** was collected: yield 45 g (88%); mp 110–115°; $[\alpha]^{25}D$ +42.0° (*c* 1, DMF).

Anal. Calcd for $C_{39}H_{41}NO_9$: C, 70.18; H, 6.19; N, 2.10. Found: C, 70.41; 5.96; N, 2.39.

Methyl 2-Benzamido-2-deoxy-3-*O*-[D-1-(methoxycarbonyl)-ethyl]-β-D-glucopyranoside 4-Acetate (2c).—To a solution of 10 g (0.015 mol) of **2b** in 143 ml of glacial acetic acid heated to 90° was added dropwise 157 ml of water.[9] During the addition, solid began to separate. After the addition was complete (20 min), the mixture was heated for an additional 20 min at 90° and then cooled for 2 hr at 0°. The precipitated solid was collected on a filter funnel and washed with 50% acetic acid. The filtrate was then evaporated to dryness and the residue was heated with toluene *in vacuo* to remove the last traces of water. Finally, the solid was recrystallized from isopropyl alcohol, giving 3.6 g (57.3%) of **2c**: mp 206–208°; $[\alpha]^{25}D$ +39.1° (*c* 1, DMF).

Anal. Calcd for $C_{20}H_{27}NO_9$: C, 56.40; H, 6.40; N, 3.29. Found: C, 56.43; H, 6.69; N, 3.44.

Methyl 2-Benzamido-2-deoxy-3-*O*-[D-1-(methoxycarbonyl)-ethyl]-β-D-glucopyranoside 4-Acetate 6-Methanesulfonate (2d).—To 84 ml of dry pyridine at −10° was added dropwise 225 ml of methanesulfonyl chloride.[9] After the addition was complete, 3.9 g (0.00918 mol) of **2c** was added in five portions over a 15-min period and the solution was left at 5° overnight. The solution was then poured into 500 ml of ice–water and scratched, whereupon solid separated. After cooling for 30 min, the solid was collected, washed repeatedly with water, and dried. The material was recrystallized from ethyl alcohol, giving 3 g (71.5%) of **2d**: mp 184° dec; $[\alpha]^{25}D$ +29.9° (*c* 1, DMF).

Anal. Calcd for $C_{21}H_{29}NO_{11}S$: C, 50.20; H, 5.82; N, 2.78; S, 6.37. Found: C, 49.89; H, 5.73; N, 2.61; S, 6.37.

Reaction of 2d with Tetrabutylammonium Fluoride.—A solution of 100 mg (0.198 mmol) of **2d** and 300 mg (1.17 mmol) of tetrabutylammonium fluoride in 5 ml of methyl ethyl ketone was refluxed for 48 hr. The solvent was removed *in vacuo* and the residual oil was dissolved in 50 ml of chloroform and extracted twice with 200 ml of water. The organic layer was dried, the solvent was removed *in vacuo*, and the residue was dissolved in isopropyl alcohol. Upon cooling, a solid formed: yield 40 mg; mp 172–174°; nmr (DMSO) δ 2 and 2.07 ($2CH_3COO$). This material could not be separated into its two components.

Methyl 2-Benzamido-2-deoxy-3-*O*-[D-1-(methoxycarbonyl)-ethyl]-β-D-glucopyranoside 6-*p*-Toluenesulfonate (2f).—To 300

(7) All melting points were run according to the USP procedure and are uncorrected. Analyses and melting points were performed by the staff of M. E. Auerbach and K. D. Fleischer. Nmr spectra were determined on a Varian A60 spectrophotometer and the mass spectra on a Jeolco double-focusing high-resolution mass spectrometer, by R. K. Kullnig and S. Clemans.

(8) R. Gigg, P. M. Carroll, and C. D. Warren, *J. Chem. Soc.*, 2975 (1965).

(9) P. H. Gross, K. Brendel, and H. K. Zimmerman Jr., *Justus Liebigs Ann. Chem.*, **688**, 175 (1965).

ml of pyridine which was cooled to −10° was added 8.43 g (0.00465 mol) of *p*-toluenesulfonyl chloride.[10] After the addition was complete, 15 g (0.00353 mol) of **2a** was added in five portions over a 15-min period. After stirring at −10° for 1 hr, the solution was left at 5° overnight and then poured into 2 l. of water with stirring, and the solid which separated was collected, washed with water, and dried, giving 18.6 g (71.5%) of **2f**: mp 80–83°; $[\alpha]^{25}D$ +22.4° (*c* 1, DMF).

Anal. Calcd for $C_{25}H_{31}NO_{10}S$: C, 55.85; H, 5.81; S, 5.97. Found: C, 55.89; H, 5.76; S, 5.82.

Methyl 2-Benzamido-2-6-dideoxy-6-fluoro-3-*O*-[D-1-(methoxycarbonyl)ethyl]-β-D-glucopyranoside (3b).—A solution of 2.5 g (4.65 mmol) of **2f** and 1.46 g (5.6 mmol) of tetrabutylammonium fluoride in 100 ml of dry methyl ethyl ketone was refluxed overnight. The solvent was removed and the residue was triturated with water. A gum formed (**3b**), which was collected and dried and recrystallized from isopropyl alcohol: yield 1.074 g (60%); mp 184–186°; $[\alpha]^{25}D$ +46.1° (*c* 1, DMF); nmr (DMSO) δ 1.25–1.38 (d, 3, CH_3–), 2.40 (s, 3, CH_3OC–), 3.30 (s, 3, CH_3OC–), and 3.38 (s, 2, CH_2F).

Anal. Calcd for $C_{18}H_{24}FNO_7$: N, 3.64; F, 4.94. Found: N, 3.55; F, 5.04.

2-Amino-2,6-dideoxy-6-fluoro-3-*O*-(D-1-carboxyethyl)-D-glucopyranose Hydrochloride (4).—A mixture of 2.2 g (5.72 mmol) of **3b** and 5 ml of 3 *N* HCl was heated on a steam bath with stirring for 4 hr.[8] The brown solution was cooled in an ice bath for 30 min and the benzoic acid was separated by filtration. The filtrate was decolorized with charcoal, the solution obtained by filtration was concentrated to dryness, and the residue was heated with 50 ml of acetone. The undissolved solid was removed by filtration, the gummy material obtained by removal of the solvent was triturated with ether, and the resulting solid was collected and dried. A 1.2-g yield (85.7%) of material was obtained which could not be recrystallized and was hygroscopic, $[\alpha]^{25}D$ +64.1° (*c* 1, DMF).

Anal. Calcd for $C_9H_{16}FNO_6 \cdot HCl$: N, 4.83; Cl, 12.25. Found: N, 3.47; Cl, 11.65.

Methyl 2-Benzamido-2,6-dideoxy-6-iodo-3-*O*-(D-1-carboxyethyl)-D-glucopyranoside 4-Lactone (5a).—A solution of 2.5 g (4.34 mmol) of **2f** and 5 g (33.0 mmol) of sodium iodide in 25 ml of dry methyl ethyl ketone was heated in a pressure bottle at 110° for 6 hr.[11] After cooling to room temperature, the solid was removed by filtration and the filtrate was concentrated to dryness. The residue was triturated with water and the solid **5a** which formed was collected, dried, and recrystallized from ethyl alcohol: yield 1 g (43.5%); mp 232–234°; $[\alpha]^{25}D$ +34.3° (*c* 1, DMF); mass spectrum *m/e* 461; nmr (DMSO) δ 1.25–1.62 (3, CH_3) and 3.39 (s, 3, $-OCH_3$).

Anal. Calcd for $C_{17}H_{20}NIO_6$: N, 3.04; I, 27.53. Found: N, 3.04; I, 27.62.

Methyl 2-Benzamido-2,6-dideoxy-6-iodo-3-*O*-[D-1-(methoxycarbonyl)ethyl]-β-D-glucopyranoside (6).—A solution of 300 mg (0.612 mmol) of **5a** and 33 mg (0.612 mmol) of sodium methoxide in 25 ml of dry methyl alcohol was left at room temperature overnight. The solution was made slightly acidic with glacial acetic acid and evaporated to dryness. The white solid residue was triturated with water, collected, and recrystallized from ethyl acetate. A 100-mg yield of **6** was obtained: mp 189–191°; mass spectrum *m/e* 493; nmr (DMSO) δ 2.75 and 2.84 (singlets, 3 each, 2 CH_3O–) and 1.03–1.10 (d, 3, CH_3); $[\alpha]^{25}D$ +16.4° (*c* 1, DMF).

Anal. Calcd for $C_{18}H_{24}INO_7$: C, 43.80; H, 492; N, 2.84; I, 25.70. Found: C, 43.72; H, 4.86; N, 2.69; I, 25.56.

Methyl-2-benzamido-2,6-dideoxy-3-*O*-(D-1-carboxyethyl)-D-gluccpyranoside-4-lactone Methanolate (5b).—A solution of 6.9 g (1.48 mmol) of **5a** in 172 ml of methyl alcohol and 18 ml of triethylamine was hydrogenated with Raney nickel at 44 psi.[11] The reduction took 2 hr, after which time the catalyst was removed by filtration and the filtrate was evaporated to dryness. The solid residue was triturated with water, collected, and recrystallized from methanol, giving 3.2 g (62%) of **5b** as its methanolate: mp 199–200°; $[\alpha]^{25}D$ +15.7° (*c* 1, DMF); mass spectrum *m/e* 368.

Anal. Calcd for $C_{17}H_{21}NO_6 \cdot CH_3OH$: C, 58.85; H, 6.82; N, 3.82. Found: C, 58.84; H, 6.98; N, 3.90.

2-Amino-2,6-dideoxy-3-*O*-(D-1-carboxyethyl)-D-glucopyranose Hydrochloride (7).—The hydrolysis of **5b** was performed in the same manner as described for the preparation of **4**. A 2.2-g yield of crude product was obtained which, after recrystallization from acetone, gave 850 mg (53.5%) of **7**: mp 174–175°; $[\alpha]^{25}D$ +111.0° (*c* 1, DMF).

Anal. Calcd for $C_9H_{17}NO_6 \cdot HCl$: N, 5.14; Cl, 13.05. Found: N, 5.12; Cl, 13.26.

Registry No.—Amine (III) salt of **1a**, 23924-09-6; **1b**, 23912-19-8; **2b**, 23912-20-1; **2c**, 23912-21-2; **2d**, 23912-22-3; **2f**, 23924-03-0; **3b**, 23924-04-1; **4**, 23924-05-2; **5a**, 23924-06-3; **5b**, 23967-32-0; **6**, 23924-07-4; **7**, 23924-08-5.

(10) W. S. Cohen, D. Levy, and E. D. Bergmann, *Chem. Ind.* (London), 1802 (1964).

(11) K. Brendel, P. H. Gross, and H. K. Zimmerman, Jr., *Justus Liebigs Ann. Chem.* **691**, 192 (1966).

A Convenient Synthesis of Protected N-Methylamino Acid Derivatives

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Methylation of the amide nitrogen of selected N-benzyloxycarbonyl and N-*t*-butyloxycarbonylamino acids with methyl iodide and silver oxide in dimethylformamide gives the corresponding N-methylamino acid derivatives in excellent yield. An unprotected carboxyl group also is converted by methylation into the methyl ester. The methylation reaction was shown to occur without racemization of the amino acid. The methyl esters obtained were converted by saponification into the corresponding N-protected N-methylamino acids. The N-*t*-butyloxycarbonyl derivatives of cysteine and serine gave, upon methylation, unsaturated amino acid products.

N-Methylamino acids are constituents of several naturally occurring peptide and depsipeptide antibiotics.[1] Peptides that contain N-methylamino acids are also of interest in relation to studies of peptide conformations.[2] Suitable synthetic methods for the preparation of N-methylamino acids are, therefore, of importance pursuant to the synthesis of peptide antibiotics and of N-methylated peptides. We herein report a convenient one-step synthesis of N-monomethyl-α-amino acids suitably protected for further elaboration in peptide synthesis.

The method of choice for the preparation of optically pure N-methylamino acids involves a three-step sequence in which an N-benzylamino acid is methylated with formaldehyde–formic acid followed by reductive removal of the N-benzyl group.[3] The N-methylamino

(1) E. Schröder and K. Lübke, "The Peptides," Vol. II, Academic Press Inc., New York, N. Y. 1966, pp 397–423.

(2) J. Konnert and I. L. Karle, *J. Amer. Chem. Soc.*, **91**, 4888 (1969); J. Dale and K. Titlestad, *Chem. Commun.*, **656** (1969); V. F. Bystrov, S. L. Portnova, V. I. Tsetlin, V. T. Ivanov, and Yu A. Ovchinnikov, *Tetrahedron*, **25**, 493 (1969); M. Goodman, *Colloq. Int. Centre Nat. Rech. Sci.*, 1 (1968).

(3) P. Quitt, J. Hellerbach, and K. Vogler, *Helv. Chim. Acta*, **46**, 327 (1963).

acid thus obtained must yet be converted to an appropriately protected derivative prior to use in peptide synthesis.

It was reported[4] recently, in connection with studies on the determination of amino acid sequences in peptides using mass spectrometry, that milligram quantities of N-acyl oligopeptides can be permethylated by treatment with methyl iodide and silver oxide in dimethylformamide. The above reaction also has been applied to the permethylation of peptides substituted with N-benzyloxycarbonyl or N-*t*-butyloxycarbonyl groups.[5] We report in this paper the application of the above methylation procedure on a preparative scale to the readily available and widely used N-benzyloxycarbonyl- and N-*t*-butyloxycarbonyl-L-amino acid derivatives of monoamino monocarboxylic acids. This reaction effects methylation of the amide nitrogen and affords in one step and in nearly quantitative yield the corresponding optically active N-methylamino acid derivatives (Tables I and II). An unprotected carboxyl group also undergoes methylation to give the corresponding methyl ester. The N-methylamino acid derivatives listed in Table I were obtained as oils that appeared to be homogeneous as shown by thin layer chromatography and nmr spectral data. Since N-methylamino acid derivatives generally show poor crystalline properties, the homogeneity of the products obtained is an important aspect of the method.

Table I

Methylation of N-Benzyloxycarbonyl- and N-*t*-Butyloxycarbonyl-L-amino Acids with Methyl Iodide and Silver Oxide in Dimethylformamide

Reactant	Product	Yield, %
Z-Ala-OH (1)[a]	Z-MeAla-OMe (2)	94
Z-Phe-OH (3)	Z-MePhe-OMe (4)	97
Z-Val-OBzlNO$_2$ (5)	Z-MeVal-OBzlNO$_2$ (6)	93
Boc-Ala-OH (7)	Boc-MeAla-OMe (8)	94
Boc-Ile-OH (9)	Boc-MeIle-OMe (10)	98
Boc-Val-OH (11)	Boc-MeVal-OMe (12)	94

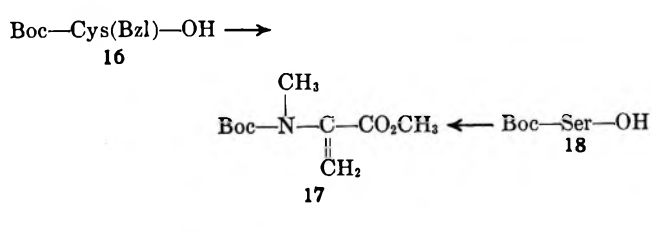
[a] Abbreviations used are those recommended by the IUPAC-IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241**, 2491 (1966).

Spectral data obtained for the methylated products were consistent with the assigned structures. The infrared spectra lacked absorption due to amide NH or carboxyl OH in the region of 3200–3600 cm^{-1} indicative of complete methylation, while possessing two carbonyl bands assignable to ester and urethan functions. In the nmr spectra, a singlet at approximately τ 7.1 due to the N-methyl protons was observed in all cases. A singlet at τ 6.3 typical of an O-methyl group was present in the spectra of the methyl esters.

The N-methylamino acid derivatives were further characterized by conversion to and comparison with known compounds. Thus, **2** gave upon saponification N-benzyloxycarbonyl-N-methyl-L-alanine (**13**);[6] likewise, **4**, **6**, and **8**, upon removal of the protective groups, yielded N-methyl-L-phenylalanine, N-methyl-L-valine, and N-methyl-L-alanine trifluoroacetate, respectively. That no appreciable racemization had occurred upon methylation was established by comparison of the specific rotations of the above deprotected N-methylamino acids with reported rotations (Table II).

The N-benzyloxycarbonyl- and N-*t*-butyloxycarbonyl-N-methylamino acid methyl esters obtained were converted by mild saponification of the ester function to the corresponding optically pure N-protected amino acids. The nmr spectra of the resulting acids showed the disappearance of the singlet at approximately τ 6.3 due to the methyl ester protons, while the infrared spectra possessed absorption typical of carboxylic acids. Thus, N-benzyloxycarbonyl- and N-*t*-butyloxycarbonylamino acids can be converted by a two-step procedure of methylation and saponification to N-methylamino acid derivatives appropriately protected for direct use in peptide synthesis.[7]

The methylation reaction appears to be most applicable for the preparation of N-methylamino acid derivatives of monoamino monocarboxylic acids not containing other functional groups capable of undergoing methylation. Previous studies[5] have indicated various difficulties attendant with the permethylation of peptides containing arginine, aspartic acid, glutamic acid, methionine, serine, or threonine. In the present study, attempts to prepare N-methylamino acid derivatives of cysteine or serine were without success. Treatment of N-*t*-butyloxycarbonyl-*S*-benzyl-L-cysteine (**16**) or the corresponding L-serine derivative **18** yielded a mixture of products as shown by thin layer chromatography. The only ninhydrin-positive material present in the mixtures was shown to be the dehydroalanine derivative **17**. The ultraviolet spectrum of **17** had maximum absorption at 240 mμ consistent with that reported[8] for similar dehydroalanine derivatives. The nmr spectrum of **17** showed two one-proton singlets at τ 4.16 and 4.63 assignable to olefinic hydrogens, while absorption due to the S-benzyl group was not present. Hydrogenation[9] of **17** over platinum oxide yielded material shown to be chromatographically (tlc) and spectrally (ir, nmr) indistinguishable from methyl N-*t*-butyloxycarbonyl-N-methyl-L-alaninate (**8**). The formation of **17** in the methylation reaction can be rationalized by an elimination reaction of an intermediate sulfonium or oxonium salt.



The N-methylamino acids commonly found in peptide antibiotics are most often derived from monoamino monocarboxylic acids.[1] Methylation with methyl iodide–silver oxide, therefore, offers a convenient synthetic route to protected derivatives of the N-methylamino acids present in peptide antibiotics.

(4) B. C. Das, S. D. Géro, and E. Lederer, *Biochem. Biophys. Res. Commun.*, **29**, 211 (1967).

(5) D. W. Thomas, B. C. Das, S. D. Géro, and E. Lederer, *ibid.*, **32**, 199 (1968); **32**, 519 (1968). K. L. Agarwal, R. A. W. Johnstone, G. W. Kenner, D. S. Millington, and R. C. Shepard, *Nature*, **219**, 498 (1968).

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(7) For leading references to methods used for peptide formation with N-methylamino acid derivatives, see E. Schröder and K. Lübke, "The Peptides," Vol. I, Academic Press Inc., New York, N. Y., 1965, pp 143, 144.

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TABLE II

SPECIFIC ROTATIONS OF N-METHYL-L-AMINO ACID DERIVATIVES

N-Methylamino acid ester	$[\alpha]^{a}D$, deg	N-Protected N-methylamino acid	$[\alpha]^{a}D$, deg	Deprotected N-methylamino acid	$[\alpha]^{a}D$, deg	Lit. $[\alpha]^{a}D$, deg
Z-MeAla-OMe (2)	−30	Z-MeAla-OH (13)	−31			−33.1[b]
Z-MePhe-OMe (4)	−77	Z-MePhe-OH (14)	−67	H-MePhe-OH	+48	+49.3[c]
Z-MeVal-OBzlNO_2 (6)	−59			H-MeVal-OH	+32	+33[c]
Boc-MeAla-OMe (8)	−40	Boc-MeAla-OH (15)	−29	$TFA^-H_2^+$-MeAla-OH	+5	+5[d]

[a] See Experimental Section for conditions of temperature, concentration, and solvent. [b] Reference 6. [c] Reference 3. [d] Determined from an authentic sample; see Experimental Section.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared spectra were obtained with a Beckman IR-8 spectrophotometer. The nmr spectra were recorded at 60 MHz on a Varian A-60 spectrometer. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Solvents were removed *in vacuo* on a Buchler rotary evaporator at bath temperatures below 40°.

Thin layer chromatographic data were obtained upon Brinkmann silica gel precoated plates in the following ascending solvent systems: R_{fA}, ligroin (bp 60–90°)-ethyl acetate (15:2); R_{fB}, chloroform–acetic acid (95:5); and R_{fC}, chloroform–methanol–acetic acid (85:10:5). Spots were detected with ninhydrin spray reagent after the developed plate had been treated with hydrochloric acid vapors.[10] To develop spots due to N-methylamino acids, it was necessary to heat the plate at 110° for 2–4 min. Where applicable, the spots were also viewed under ultraviolet light on silica gel F_{254} plates.

The silver oxide used was of reagent grade purchased from Matheson Coleman and Bell. The dimethylformamide was reagent grade and was distilled from calcium oxide. The N-benzyloxycarbonyl- and N-*t*-butyloxycarbonylamino acids employed were purchased commercially.

General Procedure for Methylation of N-Protected Amino Acid Derivatives.—The N-benzyloxycarbonyl- or N-*t*-butyloxycarbonylamino acid was dissolved in anhydrous dimethylformamide. To the resulting solution was added methyl iodide (four- to eightfold molar excess) and silver oxide (three- to fourfold molar excess.) The reaction mixture was stirred magnetically at room temperature for 5–8 hr in case of the N-benzyloxycarbonyl derivatives, while for the N-*t*-butyloxycarbonylamino acids the reaction mixture was stirred at 45° for several hours. The mixture was filtered and the solid washed with a small volume of dimethylformamide. To the filtrate was added approximately a fourfold volume of chloroform. The chloroform phase, in which a precipitate had formed, was washed twice with 5% aqueous potassium cyanide, several times with water, and was dried over magnesium sulfate. The drying agent was removed by filtration and the solvent evaporated *in vacuo*. The last traces of dimethylformamide usually present were removed *in vacuo* with an oil vacuum pump at a bath temperature below 40°. The methylated products were obtained in good yield as chromatographically homogeneous oils.

Methyl N-Benzyloxycarbonyl-N-methyl-L-alaninate (2).—A solution of 3 g (13.5 mmol) of 1 in 40 ml of anhydrous dimethylformamide was stirred at room temperature with 7 ml (108 mmol) of methyl iodide and 12.5 g (54 mmol) of silver oxide for 8 hr. There was obtained 3.2 g (94%) of a clear oil: tlc R_{fA} 0.29, R_{fB} 0.74; ir (film) no NH or OH absorption at 3600–3200, 1725, 1685 cm^{-1} (C=O); nmr ($DCCl_3$) τ 2.66 (s, 5 H, phenyl), 4.85 (s, 2 H, benzyl), 5.25 (s, 1 H, α proton), 6.34 (s, 3 H, methyl ester), 7.12 (s, 3 H, N-methyl), 8.61 (d, J = 7.5 Hz, 3 H, α-methyl protons). An analytical sample was prepared by short-path distillation, bp 110–113° (0.1 mm), $[\alpha]^{24}D$ −30° (*c* 1.0, AcOH).

Anal. Calcd for $C_{13}H_{17}NO_4$ (251.2): C, 62.2; H, 6.82; N, 5.58. Found: C, 61.9; H, 7.01; N, 5.43.

Treatment of 0.237 g (1 mmol) of methyl N-benzyloxycarbonyl-L-alaninate as above gave 0.20 g (81%) of an oil indistinguishable chromatographically and spectrally from 2.

Methyl N-Benzyloxycarbonyl-N-methyl-L-phenylalaninate (4).—A solution of 3 (2.0 g, 6.7 mmol) in 30 ml of anhydrous dimethylformamide was stirred at room temperature with 1.7 ml (27.6 mmol) of methyl iodide and 4.66 g (20.1 mmol) of silver oxide for 8 hr. A pale yellow oil (2.04 g, 97% yield) was obtained: tlc R_{fA} 0.33, R_{fB} 0.64; ir (film) no absorption 3200–3600, 1730, and 1685 cm^{-1} (C=O); nmr ($DCCl_3$) τ 2.75 (m, 10 H, phenyl groups), 4.92 (s, 2 H, O-benzyl), 5.1 (m, 1 H, α hydrogen), 6.30 (s, 3 H, methyl ester), 6.76 (d, 2 H, α-benzyl), 7.18 (s, 3 H, N-methyl); $[\alpha]^{24}D$ −77° (c 1.6, EtOH). An analytical sample was prepared by chromatography of the oil on neutral alumina and elution with hexane–ethyl acetate (98:2).

Anal. Calcd for $C_{19}H_{21}NO_4$ (327.4): C, 69.8; H, 6.48; N, 4.28. Found: C, 69.8; H, 6.74; N, 4.23.

***p*-Nitrobenzyl-N-benzyloxycarbonyl-L-valinate (5).**—This compound was prepared according to the procedure of Schwarz and Arakawa.[11] A solution of N-benzyloxycarbonyl-L-valine (5.02 g, 20 mmol), *p*-nitrobenzyl bromide (6.48 g, 30 mmol), and triethylamine (4.2 ml, 30 mmol) in 150 ml of ethyl acetate was heated at reflux for 16 hr. The solid was filtered and to the hot filtrate was added 2.5 ml of methanol. The cooled organic phase was washed once with cold water, three times with 1 *N* hydrochloric acid, once with water, three times with 1 *M* sodium bicarbonate, and three times with saturated sodium chloride, and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* yielded 6.86 g (89%) of pale yellow crystals, mp 103–105°. Recrystallization from ethyl acetate–ligroin (bp 60–90°) gave white crystals: mp 104.5–105.5°; ir ($CHCl_3$) 3420 (N—H), 1725 (C=O), 1520 and 1350 cm^{-1} (NO_2); nmr ($DCCl_3$) τ 2.26 (center of AB pattern, 4 H, nitro phenyl), 2.77 (s, 5 H, phenyl), 4.84 (s, 2 H, benzyl), 4.97 (s, 2 H, benzyl), 5.73 (m, 1 H, α hydrogen), 7.90 (m, 1 H, methine hydrogen), 9.14 (pair d, 6 H, nonequivalent isopropyl methyl groups).

Anal. Calcd for $C_{20}H_{22}N_2O_6$ (386.4): C, 62.2; H, 5.75; N, 7.25. Found: C, 62.6; H, 5.76; N, 7.46.

***p*-Nitrobenzyl N-Benzyloxycarbonyl-N-methyl-L-valinate (6).**—One gram (2.6 mmol) of 5 in 8 ml of anhydrous dimethylformamide was treated with 4 ml (64.8 mmol) of methyl iodide and 0.6 g (2.6 mmol) of silver oxide for 5 hr at room temperature. If the reaction was carried out on a larger scale or allowed to proceed for longer periods of time, multiple spots were observed upon thin layer chromatography. There was obtained from the reaction 0.97 g (93%) of a light yellow oil: tlc R_{fA} 0.23, R_{fB} 0.90; ir (CCl_4) no absorption 3600–3200, 1730 and 1700 (C=O), 1530 and 1350 cm^{-1} (NO_2); nmr ($DCCl_3$) τ 2.25 (center of AB pattern, nitrophenyl, 4 H), 2.73 (s, 5 H, phenyl), 4.82 (s) and 4.87 (s) (total 4 H, benzyl groups), 5.53 (m, 1 H, α hydrogen), 7.10 (s, 3 H, N-methyl), 7.78 (m, 1 H, isopropyl methine), 9.05 (pair of d, 6 H, nonequivalent isopropyl protons); $[\alpha]^{25}D$ −59° (*c* 1.0, AcOH); parent peak *m/e* 400, 100% *m/e* 91. An analytical sample was prepared by chromatography of the oil on neutral alumina and elution with hexane-ethyl acetate (3:1).

Anal. Calcd for $C_{21}H_{24}N_2O_6$ (400.4): C, 63.0; H, 6.05; N, 6.98. Found: C, 62.7; H, 6.31; N, 6.98.

Methyl N-*t*-Butyloxycarbonyl-N-methyl-L-alaninate (8).—A mixture of 7 (1.0 g, 5.3 mmol), methyl iodide (2.6 ml, 42.4 mmol), and silver oxide (4.9 g, 21.2 mmol) in 25 ml of anhydrous dimethylformamide was stirred at 45° for 5 hr, followed by continued stirring at room temperature for 14 hr. Following work-up of the reaction mixture, there was obtained 1.08 g (94%) of a clear oil: tlc R_{fA} 0.39, R_{fB} 0.71; ir (CCl_4) no OH or NH absorption 3600–3200, 1735 and 1695 cm^{-1} (C=O); nmr ($DCCl_3$) τ 5.35 (m, 1 H, α hydrogen), 6.29 (s, 3 H, methyl ester), 7.17 (s, 3 H, N-methyl), 8.56 (s, 9 H, *t*-butyl), 8.63 (d, 3 H, α-methyl group with one peak of doublet superimposed on peak due to *t*-butyl group); $[\alpha]^{26}D$ −40° (c 2.1, ethanol). An analytical

(10) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis," W. H. Freeman and Co., San Francisco, Calif., 1969, p 62.

(11) H. Schwarz and K. Arakawa, *J. Amer. Chem. Soc.*, **81**, 5691 (1959).

sample was prepared by short-path distillation, bp 105–108° (20 mm).

Anal. Calcd for $C_{10}H_{19}NO_4$ (217.2): C, 55.2; H, 8.82; N, 6.45. Found: C, 55.0; H, 8.70; N, 6.55.

Methyl N-*t*-Butyloxycarbonyl-N-methyl-L-isoleucinate (10).—A mixture of **9** (1.0 g, 4.33 mmol), methyl iodide (1.1 ml, 17.3 mmol), and silver oxide (3.04 g 13.0 mmol) in 20 ml of anhydrous dimethylformamide was stirred at 45° for 18 hr. Work-up of the reaction mixture yielded 1.10 g (98%) of clear liquid: tlc R_{fA} 0.70, R_{fB} 0.83; ir (film) no OH or NH absorption 3600–3200, 1730 and 1685 cm^{-1} (C=O); nmr ($DCCl_3$) τ 5.58 (m, 1 H, α hydrogen), 6.27 (s, 3 H, methyl ester), 7.16 (s, 3 H, N-methyl), 8.0 (brd m, 1 H, methine), 8.55 (s, 9 H, *t*-butyl), 9.0–9.2 (m, 8 H, isoleucyl group protons); parent peak *m/e* 259; $[\alpha]^{29}D$ −86° (c 1.94, EtOH). An analytical sample was prepared by short-path distillation, bp 82° (0.1 mm).

Anal. Calcd for $C_{13}H_{25}NO_4$ (259.3): C, 60.2; H, 9.74; N, 5.41. Found: C, 60.3; H, 9.78; N, 5.75.

Methyl N-*t*-Butyloxycarbonyl-N-methyl-L-valinate (12).—A solution of **11** (3.0 g, 13.8 mmol) in 40 ml of anhydrous dimethylformamide was stirred with 16.0 g (113 mmol) of methyl iodide and 12.3 g (53 mmol) of silver oxide at 45° for 16 hr to yield 3.19 g (94%) of **12** as a clear liquid: tlc R_{fA} 0.49, R_{fB} 0.73; ir (film) no absorption 3200–3600, 1730 and 1690 cm^{-1} (C=O); nmr ($DCCl_3$) τ 5.75 (m, 1 H, α hydrogen), 6.30 (s, 3 H, methyl ester), 7.17 (s, 3 H, N-methyl), 7.80 (m, 1 H, methine), 8.55 (s, 9 H, *t*-butyl), 9.07 (pair d, 6 H, nonequivalent isopropyl methyl groups); $[\alpha]^{24}D$ −51° (c 2.1, EtOH). An analytical sample was prepared by short-path distillation, bp 77° (0.3 mm).

Anal. Calcd for $C_{12}H_{23}NO_4$ (245.3): C, 58.8; H, 9.45; N, 5.71. Found: C, 58.7; H, 9.54; N, 5.95.

N-Benzyloxycarbonyl-N-Methyl-L-alanine (13).—A solution of **2** (1.5 g, 6.0 mmol) and 6.2 ml of 1 *N* sodium hydroxide in 20 ml of 95% ethanol was allowed to stand at room temperature for 1 hr. The major portion of the solvent was evaporated *in vacuo*, after which 15 ml of water was added. The resulting solution was cooled and acidified to pH 3 with 1 *N* hydrochloric acid. The aqueous phase was extracted three times with ethyl acetate, following which the organic phase was washed several times with water and dried over magnesium sulfate. The drying agent was filtered and the solvent removed *in vacuo* to yield 1.13 g (80%) of an oil that slowly solidified upon standing, mp 59.5–64.0°. Recrystallization from benzene–hexane gave white crystals melting at 62.0–64.0° (lit.[6] 62.0–64.5°); tlc R_{fB} 0.45, R_{fC} 0.68; nmr ($DCCl_3$) τ 2.67 (s, 5 H, phenyl), 4.84 (s, 2 H, benzyl), 5.2 (m, 1 H α-hydrogen), 7.08 (s, 3 H, N-methyl), 8.58 (d, J = 7.5 Hz, 3 H, α-methyl protons); $[\alpha]^{28}D$ −31° (c 2, AcOH) {lit.[6] $[\alpha]^{28}D$ −33.1 (c 2, AcOH)}.

N-Benzyloxycarbonyl-N-methyl-L-phenylalanine (14).—A solution of **4** (2.92 g, 8.9 mmol) and 10.0 ml (10 mmol) of 1 *N* sodium hydroxide in 35 ml of ethanol (room temperature, 2.5 hr) was saponified as described above for **13** to yield 2.20 g (79%) of an oil that slowly solidified upon standing, mp 65–70°. Three recrystallizations from ethyl acetate–hexane gave crystals melting at 67–71°: tlc R_{fB} 0.45, R_{fC} 0.69; ir (film) 3400–2500 (carboxyl OH), 1700 cm^{-1} (C=O); nmr ($DCCl_3$) τ 0.10 (s, 1 H, carboxyl hydrogen), 2.75 and 2.80 (2 s, 10 H, phenyl groups), 4.92 (s, 2 H, O-benzyl), 5.1 (m, 1 H, α hydrogen), 6.75 (m, 2 H, α-benzyl), 7.21 (s, 3 H, N-methyl); $[\alpha]^{28}D$ −67° (c 1.8, EtOH).

Anal. Calcd for $C_{18}H_{19}NO_4$ (313.3): C, 69.1; H, 6.11; N, 4.47. Found: C, 69.2; H, 6.04; N, 4.38.

N-*t*-Butyloxycarbonyl-N-methyl-L-alanine (15).—A solution of **8** (0.60 g, 2.77 mmol) and 3 ml of 1 *N* sodium hydroxide in 15 ml of ethanol was saponified as described for **13** to give 0.37 g (66%) of crystals. Recrystallization from ligroin gave material melting at 89–91° (lit.[12] 89°): tlc R_{fB} 0.47, R_{fC} 0.71, ir (film) 3500–2500 (carboxyl OH), 1725, 1650 (C=O); nmr ($DCCl_3$) τ 5.34 (m, 1 H, α hydrogen), 7.15 (s, 3 H, N-methyl), 8.55 (s, 9 H, *t*-butyl), 8.60 (d, 3 H, α-methyl); $[\alpha]^{26}D$ −29° (c 1.0, EtOH).

Anal. Calcd for $C_9H_{17}NO_4$ (203.2): C, 53.3; H, 8.42; N, 6.90. Found: C, 53.2; H, 8.67; N, 6.82.

(12) S. L. Portnova, V. F. Bystrov, V. I. Testlin, V. T. Ivanov, and Yu. A. Ovchinnikov, *Zh. Oshch. Khim.*, **38**, 428 (1968).

Conversion of *p*-Nitrobenzyl N-Benzyloxycarbonyl-N-methyl-L-valinate (6) to N-Methyl-L-valine.—The hydrogenolysis of **6** was carried out following the procedure described by Schwarz and Arakawa.[11] One gram (2.5 mmol) of **6** was dissolved in 20 ml of 1:1 ethyl acetate–methanol. To this solution was added 4.0 ml of 1 *N* hydrochloric acid and 0.30 g of 10% palladium on charcoal. The reaction mixture was hydrogenated at 15 psi of hydrogen for 2 hr. The catalyst was filtered and washed with methanol. To the filtrate was added 5.7 ml of triethylamine and the solvent was removed *in vacuo* to yield a yellow oil. The oil was dissolved in 5 ml of hot water followed by the addition of 75 ml of ethanol. The white crystals, which formed upon cooling, were collected by filtration and allowed to air dry (0.17 g, 51%). The solid material obtained was chromatographically indistinguishable from an authentic sample of N-methyl-L-valine: $[\alpha]^{30}D$ −32° (c 1.7, 6 *N* HCl) {lit.[3] $[\alpha]D$ +33° (c 1, 6 *N* HCl)}.

Conversion of N-Benzyloxycarbonyl-N-methyl-L-phenylalanine (12) to N-Methyl-L-phenylalanine.—A solution of **12** (0.45 g, 1.43 mmol) in 30 ml of 1:1 ethyl acetate–methanol containing 2.2 ml of 1 *N* hydrochloric acid and 0.17 g of 10% palladium on charcoal was hydrogenated at 18 psi of hydrogen for 2 hr. Treatment as described above for the hydrogenolysis of **6** gave 0.23 g (90%) of a white solid. This material was recrystallized once from water: mp 255–260° dec (lit.[3] 260° dec); $[\alpha]^{26}D$ +48° (c 1.0, 1 *N* NaOH) {lit.[3] $[\alpha]D$ +49.3° (c 1.0, 1 *N* NaOH)}.

Conversion of N-*t*-Butyloxycarbonyl-N-methyl-L-alanine (15) to N-Methyl-L-alanine Trifluoroacetate.—A solution of **13** (107 mg) was allowed to stand at room temperature for 2 hr in 10 ml of trifluoroacetic acid. Removal of the solvent *in vacuo* yielded a clear oil. The oil was dissolved in 3 ml of ethyl acetate followed by the addition of 3 ml of ligroin. White crystals formed within minutes upon standing. After cooling, the crystals were filtered, washed with 1:1 ethyl acetate–ligroin, and air-dried. There was obtained 140 mg (120%) of product, mp 135–136.5°, $[\alpha]^{28}D$ +5° (c 2, EtOH).

Treatment of N-methyl-L-alanine (Cyclo Chemical) with trifluoroacetic acid as above gave the same compound: mp 135–136.5°; mmp 135–136°; $[\alpha]^{28}D$ +5° (c 2, EtOH).

Anal. Calcd for $C_6H_{10}F_3NO_4$ (217.1): C, 33.2; H, 4.61; N, 6.46. Found: C, 33.3; H, 4.74; N, 6.58.

Methylation of *S*-Benzyl-N-*t*-butyloxycarbonyl-L-cysteine.—The cysteine derivative **16** (0.50 g, 1.6 mmol) was treated with 1.1 ml (17.3 mmol) of methyl iodide and 2.0 g (8.95 mmol) of silver oxide at 27° for 6 hr as described above in the general procedure to yield 0.36 g of a clear oil. Tlc showed one ninhydrin-positive spot, R_{fA} 0.35; however, four spots were visible under ultraviolet light. Short-path distillation gave 0.18 g of a clear oil that was shown by tlc to still contain small amounts of two materials having higher R_f values than the major ninhydrin-sensitive material: uv max (cyclohexane) 240 mμ; nmr ($DCCl_3$) τ 2.61 (weak peak due to impurity), 4.16 (s, 1 H, vinyl proton), 4.63 (s, 1 H, vinyl proton), 6.21 (s, 3 H, methyl ester), 6.87 (s, 3 H, N-methyl), 8.58, (s, 9 H, *t*-butyl); $[\alpha]^{25}D$ 0° (c 1, EtOH). Hydrogenation of **17** (120 mg) at 20 psi of hydrogen over platinum oxide (65 mg) at room temperature for 4.5 hr gave **8** as established by comparison of tlc, ir, and nmr data.

N-*t*-Butyloxycarbonyl-L-serine (**18**), when treated with methyl iodide–silver oxide in dimethylformamide, yielded results similar to those obtained above for the corresponding cysteine derivative **16**.

Registry No.—**2**, 24164-72-5; **4**, 24164-73-6; **5**, 5276-76-6; **6**, 24164-75-8; **8**, 24164-04-3; **10**, 24164-05-4; **12**, 24164-06-5; **13**, 21691-41-8; **14**, 2899-07-2; **15**, 16948-16-6; N-methyl-L-alaninetrifluoroacetate, 24164-10-1.

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(S)-13-Hydroxy-*cis*-9,*trans*-11-octadecadienoic Acid Lactone, a 14-Membered-Ring Compound from *Monnina emarginata* Seed Oil

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The oil extracted from *Monnina emarginata* seed contained 4% (*S*)-13-hydroxy-*cis*-9,*trans*-11-octadecadienoic acid lactone, coriolide, a 14-membered-ring lactone. Mass spectra of the hydrogenated lactone and the derived methyl ester established that the heterocyclic oxygen was bound to C-13 of an 18-carbon acid. Ozonolysis of the methyl dienoloate from the lactone demonstrated that the conjugated diene group involved carbons 9–12. The nmr spectrum verified the *cis,trans* configuration of the diene system as well as the proximity of the carboxylate oxygen to the C-13 proton. The plain-positive optical rotatory dispersion curves of the coriolide, the corresponding saturated lactone, and the derived methyl ester indicate they each have an *S* configuration.

A large number of γ- and δ-lactones have been isolated from the bark, leaves, and roots of many varieties of plants and other natural sources. However, the authors know of only one large-ring lactone that has been isolated from seed oil and described.[2] In 1927, the lactone of 16-hydroxy-7-hexadecenoic acid was obtained in small amounts from the musk-scented seed oil of *Hibiscus abelmoschus* L.[3] We wish to report the isolation of the lactone of a 13-hydroxyoctadecadienoic acid from the seed oil of *Monnina emarginata* (Polygalaceae), a plant native to Uruguay. Chemical and physical examinations of the 14-membered-ring lactone have demonstrated that it has the *S* configuration[4] and that the derived methyl ester is the enantiomer of the methyl (*R*)-coriolate [methyl (*R*)-13-hydroxy-*cis*-9,-*trans*-11-octadecadienoate] isolated and characterized by Tallent, *et al.*,[5] and by Powell, *et al.*[6]

Although the lactone, (*S*)-coriolide (**1**), was only slightly separated from the nonpolar triglycerides by thin layer chromatography in petroleum ether–ethyl ether (4:1), it had a mobility approximately twice that of the least polar glycerides in benzene and was thus obtained in amounts equivalent to 4% of the oil. The infrared spectrum of the low-melting solid had two notable features: a normal ester or lactone absorption at 1745 cm^{-1}; a conjugated *cis,trans* diene absorption in which the 982-cm^{-1} band was of reduced intensity and was broadened considerably in comparison to that of the derived methyl dienoloate (Figure 1).[7] The absorptions between 1100 and 1250 cm^{-1} show more fine structure than is normally observed for long-chain esters[8] or glycerides.[9] The presence of a conjugated diene chromophore was also indicated by the ultraviolet absorption maximum at 234 mμ, although the molar absorptivity was somewhat reduced in comparison to the related acyclic *cis,trans* dienolates.[5,6] The lack of any significant proton magnetic resonance absorption between τ 4.8 and 7.2 (Figure 2) clearly indicated that the material isolated by thin layer chromatography could not be an alkyl ester or glyceride. The optical rotatory dispersion curve of the lactone was plain positive between 600 and 255 mμ.

(*S*)-Coriolide (**1**) readily added 2 mol equiv of H_2 in the presence of Pd–C, Scheme I. The elution times of the hydrogenated lactone (**3**) were near that of methyl stearate on hydrocarbon and polyester gas–liquid chromatographic columns. A mass spectral analysis of the reduced lactone found the molecular ion peak to be *m/e* 282 as expected for a lactone of hydroxystearic acid. The principal high-molecular-weight fragments were *m/e* 264 resulting from the loss of the elements of water; *m/e* 211 derived from the cleavage of the C-13,C-14 bond producing $[CH(CH_2)_{11}C{=}O]^+$; and *m/e* 182 arising from the loss of $C_8H_{12}O$ by cleavage between C-12 and C-13 to give $[(CH_2)_{11}C{=}O]^+$. The remaining ion fragments are common to long-chain esters.[10] Thus the hydroxyl is bound to C-13 of an 18-carbon acid. Furthermore, the chromatographic retention times and the mass spectrum of **3** preclude the presence of appreciable amounts of dimers or other polymeric forms of 13-hydroxystearic acid and, thereby, of coriolic acid in the lactone fraction. The optical rotatory dispersion curve of **3**, like that of **1**, was plain positive between 600 and 250 mμ.

Sodium methoxide catalyzed transmethylation of the lactone from the seed oil produced **2**, which had the same thin layer chromatographic mobility as methyl 13-hydroxy-*cis*-9,*trans*-11-octadecadienoate. The infrared, ultraviolet, and nmr spectra of the ester were comparable to those of methyl coriolate.[5,6] The hydroxy ester **2** was ozonized, and the products were identified as described by Kleiman, *et al.*[11,12] A six-carbon aldehyde (36%), a seven-carbon hydroxyaldehyde (22%), a nine-carbon aldehydo ester (24%), and a nine-carbon diester (18%) were the major products. Thus the conjugated dienol group must comprise C-9 through C-13 of a C_{18} acid. The formation of a six-carbon aldehyde and a seven-carbon hydroxyaldehyde

(1) (a) Postdoctoral Research Associate, 1968–1970; (b) Northern Utilization Research and Development Division, Agriculture Research Service, U. S. Department of Agriculture.

(2) For an extensive review of unusual fatty acids found in plants, see C. R. Smith, Jr., "The Chemistry of Fats and Other Lipids," R. T. Holman, Ed., Pergamon Press, Oxford, in press; I. A. Wolff, *Science*, **154**, 1140 (1966).

(3) M. Kerschbaum, *Ber.*, **60**, 902 (1927), and references cited therein.

(4) R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964), and references cited therein.

(5) W. H. Tallent, J. Harris, I. A. Wolff, and R. E. Lundin, *Tetrahedron Lett.*, 4329 (1966).

(6) R. G. Powell, C. R. Smith, Jr., and I. A. Wolff, *J. Org. Chem.*, **32**, 1442 (1967).

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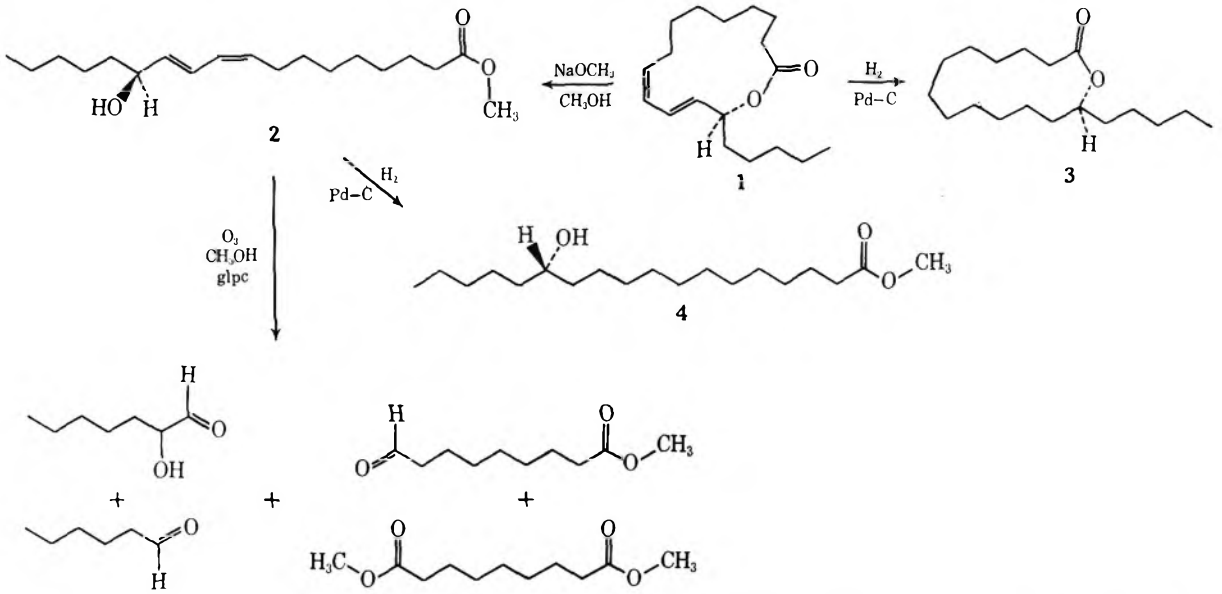
(10) R. Ryhage and E. Stenhagen, *Ark. Kemi*, **15**, 545 (1960); R. Ryhage and E. Stenhagen, in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 9.

(11) R. Kleiman, G. F. Spencer, F. R. Earle, and I. A. Wolff, *Lipids*, **4**, 135 (1969).

(12) G. F. Spencer, R. Kleiman, F. R. Earle, and I. A. Wolff, *Anal. Chem.*, **41**, 1874 (1969).

SCHEME I



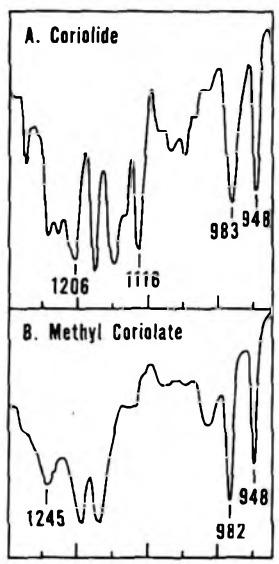


Figure 1.—Infrared spectra of (*S*)-13-hydroxy-*cis*-9,*trans*-11-octadecadienoic acid lactone [(*S*)-coriolide] and the derived methyl ester in carbon tetrachloride (10%) between 1350 and 920 cm^{-1}.

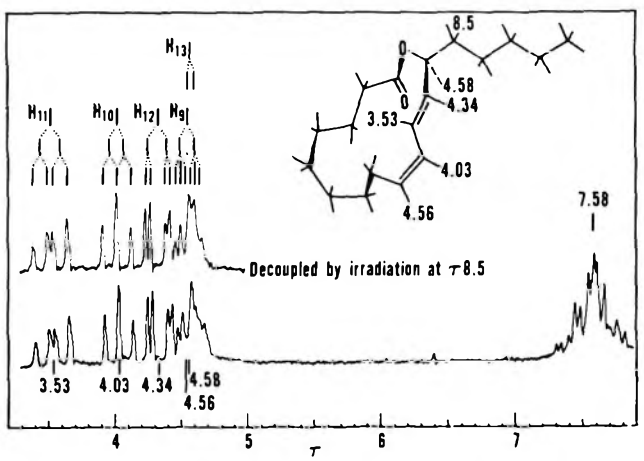


Figure 2.—Proton resonance spectrum of (*S*)-coriolide in deuteriochloroform between τ 3.2 and 7.8.

requires that the hydroxyl be bound to C-13. Ozonolysis of the coriolate isolated by Tallent, *et al.*,[12,13] yielded a similar group of compounds. The observed nmr coupling constants (Table I) indicate that the *trans* double bond must be situated between the hydroxyl group and the *cis* double bond.[5]

TABLE I
SPIN–SPIN COUPLING CONSTANTS OBSERVED IN NMR SPECTRA

	Coriolide (lactone)	Methyl coriolate (hydroxy ester)
$J_{8,9}$	~4	8
$J_{9,10}$	11	10.5
$J_{10,11}$	10.5	10.5
$J_{11,12}$	14.5	14.5
$J_{12,13}$	4	6

The specific rotation, $[\alpha]^{26.5}_{300}$ +103° (*c* 0.14, hexane), of **2** was comparable in magnitude, but opposite in sign, to that observed for methyl (*R*)-13-hydroxy-*cis*-9,*trans*-11-octadecadienoate.[5,14,15] Therefore, the hydroxy ester derived from the lactone and the lactone itself have the *S* or L configuration.[14] Methyl (*S*)-9-hydroxy-*trans*-10,*trans*-12-octadecadienoate (methyl dimorphecolate), although a member of the D family of hydroxy acids, likewise has a plain-positive optical rotatory dispersion curve between 275 and 589 mμ.[16] This similarity is as expected since the hydroxyls of methyl dimorphecolate and of the ester from the lactone have the same effective stereochemical arrangement near the active chromophore.[17]

The dienoloate derived from the lactone also absorbed 2 mol equiv of hydrogen. The R_f of the hy-

(13) W. H. Tallent, J. Harris, G. F. Spencer, and I. A. Wolff, *Lipids*, **3**, 425 (1968).

(14) C. R. Smith, Jr., in "Topics in Lipid Chemistry," Vol. I, F. D. Gunstone, Ed., Logos Press, London, in press.

(15) Unpublished results of this laboratory have demonstrated that methyl coriolate has nearly the same ORD curve in either hexane or methanol between 285 and 600 mμ.

(16) T. H. Applewhite, R. G. Binder, and W. Gaffield, *J. Org. Chem.*, **32**, 1173 (1967).

(17) (a) C. Djerassi, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heyden and Son, London, 1967, Chapter 2; (2) A. Moscowitiz, ref 17a., Chapter 3; (c) E. U. Condon, W. Setar, and H. Eyring, *J. Chem. Phys.*, **5**, 753 (1937).

droxystearate 4 was comparable to that of methyl 13-hydroxyoctadecanoate and appreciably greater than that of the 9-hydroxy isomer.[18] The mass spectrum of the hydrogenated ester was as expected for methyl 13-hydroxystearate.[10] Cleavage on each side of the hydroxy-bound carbon produced the prominent high-molecular-weight fragments, *m/e* 243, $[CH(OH)(CH_2)_{11}CO_2CH_3]^+$, and *m/e* 214, $[(CH_2)_{11}CO_2CH_3]^+$. The other major, high-molecular-weight ion, *m/e* 211, was derived from the *m/e* 243 ion fragment by the loss of the elements of methanol.[10]

In view of these results, the lactone obtained from the oil of *M. emarginata* seed must be derived from 13L-hydroxy-*cis*-9,*trans*-11-octadecadienoic acid. The nmr spectrum of the lactone (Figure 2) is in agreement with the assigned structure. The C-13 and C-9 protons were shown to resonate at τ 4.58 and 4.56, respectively, by irradiation at τ 8.5 (C-14 protons). The C-13 proton (H–C–O–) absorbed about 20 cps further downfield than the γ protons of 2-pentenoic acid γ-lactone (β-angelic acid) and the bisbutenolide of *Pterogorgia anceps*.[19] The larger shift observed for the coriolide could be caused by the close proximity of the carboxyl oxygen and the accompanying sp^2-electron cloud of the carboxylate to the C-13 proton. Both the resonance frequency and spin–spin coupling constants of the C-12 and C-13 protons differed significantly from those of the open-chain ester (Table I and Figure 2). While models of the lactone can be made to take a variety of conformations, including several with the sp^2 oxygen of the carboxyl group directed toward the center of the ring, there is only one general type of conformation without eclipsed C–H bonds and with the carbonyl oxygen directed outside the ring. Models of the lactone (Stuart–Briegleb and Dreiding type) in this conformation require that the carboxyl sp^2 oxygen bond be essentially parallel to the C-13 C–H bond and *exo* to the ring with the oxygen between 2.5 and 2.0 Å from the C-13 proton. In addition, both of the C–H bonds at C-8 are found on the *exo* side of the plane of the C-9 double bond. This conformation is consistent with the observed infrared and nmr spectra.

If the C-9 proton signal is indeed in the form of a doublet of triplets as shown in Figure 2, the dihedral angles between the two C-8 protons and the C-9 proton would be expected to be either equal (*ca.* 55 or 125°) or approximately 35 and 145°.[20] A model of the lactone can be constructed most easily with the latter conformation. Irradiation at τ 4.62 (C-9 and C-13 protons) simplified the triplet centered at τ 4.03 (C-10 proton) and the quartet at τ 4.34 (C-12 proton). Thus the protons of the lactone have resonance frequencies similar to those of methyl coriolate.[6] The coupling constants of the vinyl protons (Table I) further substantiate the geometric configuration assigned to the lactone.

The absorptivity of the diene chromophore of the lactone is *ca.* 90% of that of the related acyclic ester. A similar difference between the absorptivity of the cyclotetradecadiene (22.8×10^3) and that of the cyclooctadecadiene (24.7×10^3) has been observed.[21] Such diminutions in absorptivity have frequently been ascribed to the nonplanarity of the ground-state form of the conjugated systems.[22-25] In a study of two series of methylated aromatic carbonyls, Braude, *et al.*,[23] correlated the dipole moments of these compounds with losses of coplanarity of the carbonyl and phenyl groups. Corresponding with the changes in dipole moments were decreased molar absorptivities. Although Hubert and Dale[21] say the diene group of the cyclotetradecadiene is planar, the Braude relationship ($\cos^2\theta = \epsilon_{obsd}/\epsilon_0$)[24] suggests that the two double bonds of coriolide and those of the cyclic diene are slightly twisted, 19 and 16°, respectively, from coplanarity. The models of the lactone with the least nonbonding interaction between neighboring hydrogens also required that the conjugated diene be distorted from planarity. However, the diene group of the coriolide models could easily be made coplanar by a slight rotation of several of the carbon–carbon bonds in the ring. Hubert and Dale[21] noted that the cyclotetradecadiene is the "smallest one (cyclic diene) for which a practically strain-free molecular model can be constructed having all single bonds staggered and the correct stereochemistry[26] about the planar *cis–trans* diene grouping."

A correlation between Cotton effects in optical rotatory dispersion curves or circular dichroism measurements and the stereochemistry of a large number of γ- and δ-lactones has been made by Jennings, *et al.*[27] Beecham[28] has likewise posited a relationship based on the "chirality of the lactone ring" rather than the lactone sector rule. While extrapolation from a six-membered ring to a 14-membered one is fraught with difficulties, it is noteworthy that most of the best model of (*S*)-coriolide and the reduced lactone (**3**) fall in or near one of the positive lactone sectors[27] and has a ring chirality, as defined by Beecham,[28] that predicts a positive Cotton effect. Further, if the observation of Klyne, *et al.*,[29] that a plain positive curve precedes a positive Cotton effect holds for large-ring lactones as well as those with smaller rings, then (*S*)-coriolide appears to effect the same type of optical rotatory dispersion as has been observed for the small-ring lactones.

The magnitude of rotation of **3** is 60–70% of that of (*S*)-coriolide and is of the same sign in that portion of the spectrum which is accessible to us. In **1**, the ring with its twisted diene grouping may constitute an inherently dissymmetric chromophore, but apparently the $n \rightarrow \pi^*$ transition of the lactone grouping makes a greater contribution to the observed optical activity of **1** than do transitions associated with the diene chromophore.

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Experimental Section

Thin layer chromatographic analyses and separations utilized 0.25- or 1.0-mm layers of silica gel G[30] in benzene (solvent A) or petroleum ether (bp 40–60°)–ethyl ether (2:1) (solvent B). Preparative tlc plates were sprayed with 0.2% (w/v) solutions of 2′,7′-dichlorofluorescein in 95% ethanol, and the products were located by viewing under a uv lamp. Analytical tlc plates were sprayed with CrO_3–H_2SO_4–H_2O (2:49:49, w/v/v) and heated to 120–140° for 30 min or placed in an I_2 chamber to locate the spots. Ir spectra were determined with a Perkin-Elmer Infracord Model 337. Uv spectra were obtained in hexane with a Beckman DK-2A spectrometer. Nmr spectra were measured in deuteriochloroform solutions with a Varian HA-100 spectrometer and tetramethylsilane as an internal standard. The ORD curve and specific rotation were obtained with a Cary Model 60 recording spectropolarimeter. A Nuclide 12-90 G mass spectrometer was used to obtain the mass spectra. Glpc analyses were made on a Packard 7401 gas chromatograph equipped with dual glass columns and flame ionization detectors. One column (356 × 0.6 cm) was packed with 5% LAC-2-R-446 on Chromosorb W, acid washed, DMCS treated, and the other column (122 × 0.6 cm) was packed with 5% Apiezon L on Chromosorb W, acid washed, DMCS treated. Retention times are expressed as equivalent chain lengths (ecl).[31]

Isolation and Chromatographic Properties of Lactone 1.—Ground *M. emarginata* seed and pericarp were extracted with petroleum ether (bp 40–60°) in a Soxhlet extractor. Evaporation of the solvent left a light yellow oil in amounts equivalent to 20% of dry seed. Portions of the oil were chromatographed on 1.0-mm plates in solvent B. The triglyceride–lactone band (R_f 0.6) was scraped from the plates and eluted from the silica gel with hexane–ether (1:1) to give a mixture of glycerides and lactone in amounts equivalent to 63.4% of the seed oil recovered from the tlc plates. Rechromatography of the nonpolar glyceride–lactone mixture in benzene (1-mm plates) separated the lactone (R_f 0.5) from the glycerides (R_f 0.2–0.3). The lactone constituted 6.5% of the glyceride–lactone mixture or 4% of the recovered, fractionated seed oil. The lactone had the following properties: mp 39.5–42°; ir (CCl_4, 10%, and neat) 3010 (sh), 2935 (s), 2855 (s), 1740 (s), 1465 (m), 1445 (m), 1370 (m), 1345 (sh), 1275 (w), 1245 (m), 1229 (m), 1206 (m), 1178 (m), 1135 (sh), 1116 (m), 983 (m), 948 (m) cm^{-1} (The ratio of the intensities of the 983–948-cm^{-1} bands was 1.03; Chipault and Hawkins[7] gave a ratio of 1.20 for acyclic *cis,trans* dienes); uv max (hexane) 234 mμ (ε 23.3 × 10^3); $[\alpha]^{24}D$ +32° (*c* 2.56, hexane); ORD, $[\alpha]^{26.5}_{589}$ +27° (*c* 1.06, methanol), $[\alpha]_{550}$ +32, $[\alpha]_{500}$ +40, $[\alpha]_{450}$ +53, $[\alpha]_{400}$ +73, $[\alpha]_{350}$ +104, $[\alpha]_{300}$ +184, $[\alpha]_{280}$ +323°. Pertinent part of the nmr spectrum is displayed in Figure 2; glpc on LAC-2-R-446; ecl (relative amounts), 21.1 (36–48%), 21.4 (56–46%). The cause of the apparent isomerization during glpc analyses is unknown.

Hydrogenation of Lactone.—A 21.0-mg sample of coriolide (7.5 × 10^{-5} mol) absorbed 3.66 ml of H_2 (15.1 × 10^{-5} mol) over 10% Pd-C in hexane at 24° and atmospheric pressure. The bulk of the catalyst was removed by centrifugation. The supernatant liquid was chromatographed on a 0.25-mm layer of silica gel with benzene, and the band due to the lactone **3** was removed. The uv spectra of the recovered lactone (15 mg) did not show any maximum at 233 mμ or at longer wavelengths. The ir spectrum (CCl_4, 1%) was qualitatively the same as that of the unsaturated lactone, except for the absorptions normally associated with the olefinic groups (3010, 983, and 948 cm^{-1}). The reduced lactone, which had an ecl of 17.6 on the Apiezon L column and of 18.6 on the R-446 column, was more than 99% pure by glpc. The mass spectrum (70 eV) of the saturated lactone was *m/e* (relative intensity) 282 (3), 264 (24), 211 (28), 182 (23), 125 (13), 111 (19), 98 (39), 83 (43), 71 (19), 55 (100); ORD, $[\alpha]^{26.5}_{589}$ +20° (*c* 0.36, methanol), $[\alpha]_{550}$ +25, $[\alpha]_{500}$ +29, $[\alpha]_{450}$ +38, $[\alpha]_{400}$ +50, $[\alpha]_{350}$ +71, $[\alpha]_{300}$ +112, $[\alpha]_{250}$ +267°.

Transmethylation of Lactone.—(*S*)-Coriolide (18 mg) was mixed with 1.0 ml of 0.5 *M* $NaOCH_3$ in CH_3OH at 24° and allowed to stand with occasional shaking for 45 min. After dilution with 4 ml of salt water, the base was neutralized with dilute sulfuric acid. The products were extracted from the aqueous methanol with ether, and the extract was dried with anhydrous Na_2SO_4. Evaporation of the solvent yielded 19.2 mg of oil. Tlc of the oil in solvent B indicated two products: unreacted lactone (R_f 0.65) and a hydroxy ester (R_f 0.35) with a mobility identical with that of methyl 13-hydroxy-*cis*-9,*trans*-11-octadecadienoate. Preparative tlc (0.25-mm plate) in solvent B separated the hydroxy ester (13 mg) from the lactone (3.4 mg). The ester **2** had spectral properties essentially identical with those of known methyl coriolate:[5,6] ir (CCl_4, 10%) 3615 (sharp), 3500 (broad), 3005 (sh), 2920 (s), 2850 (s), 1735 (s), 1450 (m), 1430 (m), 1410 (w), 1370 (sh), 1360 (m), 1245 (m, broad), 1195 (m), 1170 (m), 1015 (w, broad), 982 (m), 948 (m) cm^{-1} (the ratio of the 982–948-cm^{-1} absorptivities was 1.22 in agreement with the value reported by Chipault and Hawkins[7]); uv max (hexane) 234 mμ (ε 26.3 × 10^3); nmr spectrum comparable to that reported by Tallent, *et al.*;[5] $[\alpha]^{26.5}_{300}$ +103° (*c* 0.14, hexane).

Hydrogenation of Dienoloate.—The transmethylation product, 8.8 mg (2.9 × 10^{-5} mol), absorbed 1.3 ml of H_2 (5.3 × 10^{-5} mol) at 24° under the conditions used to reduce the lactone. The resulting white solid (**4**), mp 49–50°, was found by glpc on the R-446 column to be a mixture of methyl hydroxystearate, ecl 24.8 (85%), and methyl ketostearate, ecl 24.0 (13%).[13] The mobilities of the hydrogenation products in solvent B, R_f 0.33 and 0.56, were identical with those of methyl 13-hydroxystearate and methyl 13-ketostearate, respectively. Methyl 9-hydroxystearate had an R_f of 0.22. The prominent ion fragments in the mass spectrum (70 eV) of the reduced hydroxy ester were *m/e* (relative intensity) 264 (8), 241 (41), 214 (49), 211 (84), 175 (10), 171 (18), 143 (27), 87 (67), 55 (83), 18 (100). Fragments associated with methyl 13-oxooctadecanoate[10] were observed also.

Ozonolysis of Methyl Dienoloate.—The methyl dienoloate (1 mg) was ozonized for 2 min (>11 × 10^{-6} mol of ozone/min) at room temperature in 5 ml of CH_3OH. The methanol solution (15 μl) was then injected directly on the glpc columns, and the products were identified as described by Kleiman, *et al.*[11,12] The averaged mole percentages of the four principal products (90% of peak areas) were C_8 aldehyde (36%), C_7 α-hydroxyaldehyde (22%), C_9 aldehydo ester (24%), and C_9 diester (18%).

Registry No.—**1**, 24058-12-6; **2**, 24058-13-7.

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(30) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

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Enzymic Dehydrogenation of the Lignin Model Coniferaldehyde

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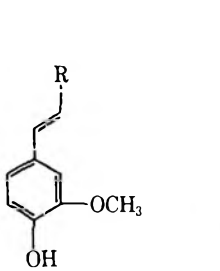
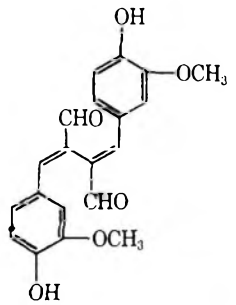
The lignin model *trans*-coniferaldehyde (**1**) was dehydrogenated in aqueous solution by peroxidase and H_2O_2. Three new dehydro dimers, 2,3-diformyl-1,4-di-5-guaiacylbuta-1,3-diene (**3**), α-(4-β-formylvinyl-2-methoxyphenoxy)coniferaldehyde (**4**), and α-(5-β-formylvinyl-2-hydroxy-3-methoxyphenyl)coniferaldehyde (**5**), were isolated. Their significance is discussed, and their nmr and mass spectra are reported.

trans-Coniferaldehyde (**1**) is considered one of the genuine monolignol precursors of lignin. It has been found in the cambial sap of various species of trees, and its incorporation into the lignin macromolecule has been demonstrated spectrally.[2,3] It has been shown to be responsible for many color reactions in lignin, and it has often been reported among the monomeric products from lignin hydrolysis. When *trans*-coniferyl alcohol (**2**) was converted to an artificial lignin by the action of air and oxidative enzymes, **1** was among the monolignols formed in the reaction, and its incorporation into dilignols and subsequently into the artificial lignin has been demonstrated.[2-4] The dehydrogenation of **1** by phenol oxidase and air has also been reported, but only the polymer formed was analyzed.[5] For these reasons we decided that it was important to investigate the low-molecular-weight products formed in the dehydrogenation reactions of **1** using peroxidase enzyme and hydrogen peroxide in aqueous medium.



1, R = CHO
2, R = CH_2OH



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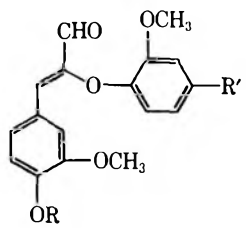
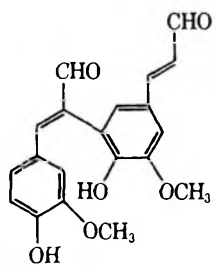
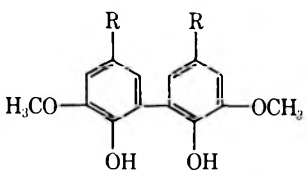


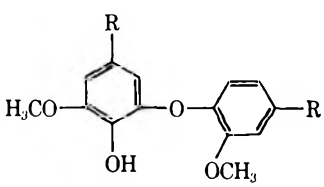
4, R = H, R′ = CH=CHCHO
14, R = OCH_3, R′ = H



5

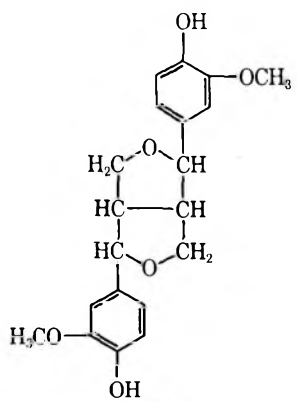


6, R = CH=CHCHO
8, R = CH=CHCH$_2$OH
10, R = $CH_2CH_2CH_2OH$

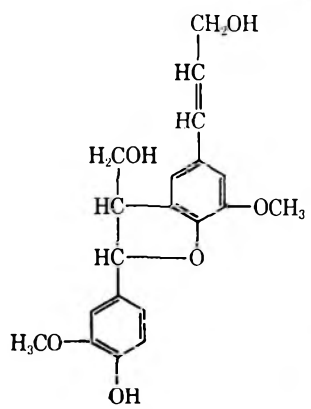


7, R = CH=CHCHO
9, R = CH=CHCH$_2$OH

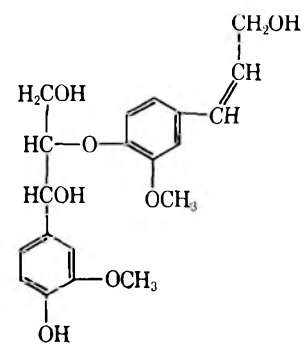
Three dimers, **3**, **4**, and **5**, were isolated from the dehydrogenation reaction mixture. A low level of incorporation of dimers of this type could well take place in natural lignin and thus with **1** contribute to the color of lignin. Tlc analysis of the whole dehydrogenation mixture at any one time showed residual **1** and dehydro dimers **3**, **4**, and **5** to be the major low-molecular-weight compounds, **3** being the predominant dimer. Determination of the yield of dimers cannot be readily undertaken owing to the extreme susceptibility of the compounds to continued oxidative polymerization. Trimers and higher oligomers were undoubtedly formed in the dehydrogenation reaction but have not been isolated. Neither the *o*,*o*′-dihydroxybiphenyl (**6**) nor the *o*-hydroxy diphenyl ether (**7**) was detected in the reaction mixture, although analogous compounds have been prominent products formed in the enzymic dehydrogenation reactions of lignin model phenols with



11



12



13

(1) Maintained at Madison, Wis., in cooperation with the University of Wisconsin.

(2) K. Freudenberg and A. C. Neish, "Constitution and Biosynthesis of *Lignin*," *Springer-Verlag, New York, N. Y., 1968.*

(3) J. M. Harkin in "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Decker, Inc., New York, N. Y., 1967, Chapter 6.

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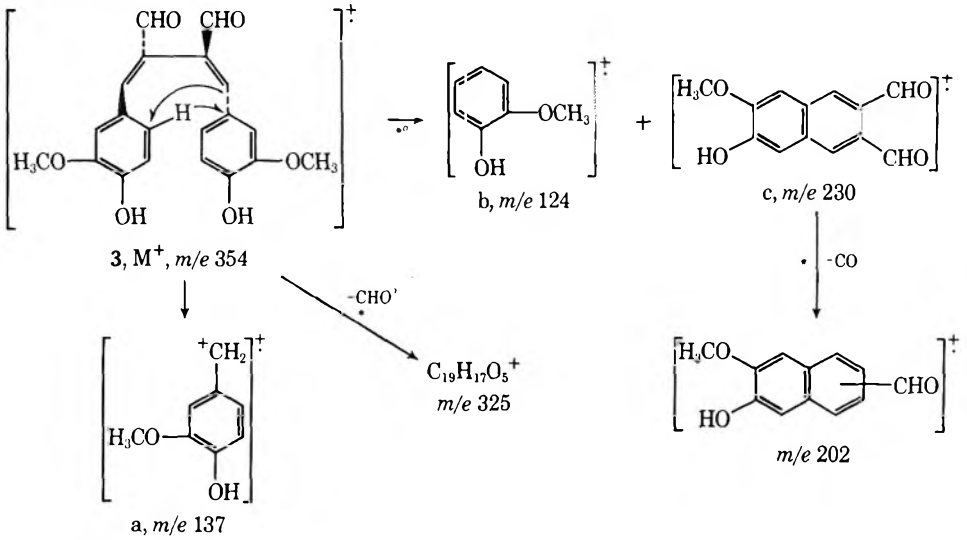
SCHEME I[a]



[a] Transitions substantiated by an appropriate metastable peak are indicated by an asterisk.

saturated side chains.[6-9] Dimers with biphenyl (**8**) and diphenyl ether (**9**) bonds were not isolated from the enzymic dehydrogenation mixture of coniferyl alcohol **2**, but the tetrahydrobiphenyl compound **10** was isolated after hydrogenation of the reaction mixture, and carboxylic acids indicating the presence of biphenyl and diphenyl ether bonds have been isolated from the degradation of methylated spruce lignin.[2,3]

Pinoresinol (**11**), dehydrodiconiferyl alcohol (**12**), and guaiacylglycerol-β-coniferyl ether (**13**) were among the major dehydro dimers formed from **2**; they have also been found in the cambial sap of spruce and other trees as well as appearing among lignin hydrolysis products.[2,3] It has been postulated that these come about first through the coupling of mesomeric forms of the phenoxyl radical, followed by the addition of a nucleophile onto the intermediate quinone methide.[2] With **13**, the nucleophile is water, and an arylglycerol-β-aryl ether is formed; with **12** and **13**, intramolecular nucleophilic addition takes place to give, respectively, the ditetrahydrofuran ring and the phenylcoumaran ring.

With compounds **3**, **4**, and **5**, however, the aldehydic side chains comprise a conjugated α,β-enone system, and the intermediate quinone methides must rearrange to stable phenol forms through loss of the acidic proton from the carbon α to the carbonyl, followed by rearomatization and protonation of the phenoxyl anion to give the dimeric compounds.

Compounds **3**, **4**, and **5** were all shown by mass spectrometry to have the molecular formula $C_{20}H_{18}O_6$. The uv and ir spectra of these indicated that each had phenolic hydroxyl and conjugated carbonyl groups.

The nmr spectrum of **3** showed two two-proton singlets at δ 7.77 and 9.66 indicating two CH=C—CHO groupings, as well as the six-proton methoxyl peak at δ 3.68 and the aromatic protons with resonance centers at δ 6.81 (d, 2, J = 8.2 Hz), 7.21 (m, 2, J = 8.2 Hz, J = 2 Hz), and 7.27 (d, 2, J = 2 Hz).

This was indicative of the presence of a β,β linkage and compatible with the structure proposed for this compound. The mass spectrum (Figure 1, Scheme I) exhibited a very prominent ion peak at m/e 137 (a),[10,11] which is ascribed to the highly characteristic benzyl ion radical. The m/e 137 (a) peak is also prominent in the mass spectra of **4** and **5**, and the analogous peak at m/e 151 is prominent in the spectra of **14**. As indicated by a metastable peak at 149.5, the molecular ion lost a neutral fragment corresponding to b to give the ion at m/e 230 (c).

Compound **4** gave a rather complex nmr spectrum. However, application of double-irradiation technique resulted in decoupling the one-proton quartet with resonance center at δ 6.60, the one-proton doublet at δ 7.37, and the one-proton doublet at δ 9.65. This revealed the presence of an ABX system on one ring (Ar—CH_A=CH_B—CH_XO) with coupling constants J_{AB} = 15.8 Hz and J_{BX} = 7.8 Hz. A one-proton singlet at δ 9.44 therefore indicated substitution on the β carbon of the formylvinyl side chain on the second ring. The singlet vinyl proton was not detectable in **4** nor in compound **14**, and was thus apparently shifted upfield into the very complex aromatic region in the spectrum of both compounds. After deuterium oxide treatment, the m/e of the molecular ion and ions d and g were increased by 1 mass unit, and the deuterium exchange ratio was calculated to be 45% for the three ions. The compound, therefore, had only one hydroxyl group. The uv spectrum in ethanol showed maxima at 243, 312, and 345 nm. When sodium hydroxide solution was added, it produced a bathochromic shift to give maxima at 309, 334, and 421 nm. The coniferaldehyde ether chromophore had a maximum *ca.* 340 nm. All of these data are compatible with structure **4**. The mass spectrum (Figure 1, Scheme II) showed two fragmentation patterns. The ether cleavages of the molecular ion produced the ions at m/e 177 (d) and 161 (e) in addition to the familiar ion at m/e 137 (a). The molecular ion also lost 57 mass units (C_2HO_2) to

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(8) J. C. Pew and W. J. Connors, *J. Org. Chem.*, **34**, 580 (1969).
(9) J. C. Pew and W. J. Connors, *ibid.*, **34**, 585 (1969).
(10) V. Kovacik, J. Skamla, D. Dusan, and B. Kosikova, *Chem. Ber.*, **102**, 1513 (1969).
(11) A. Pelter, *J. Chem. Soc., C*, 1376 (1967).

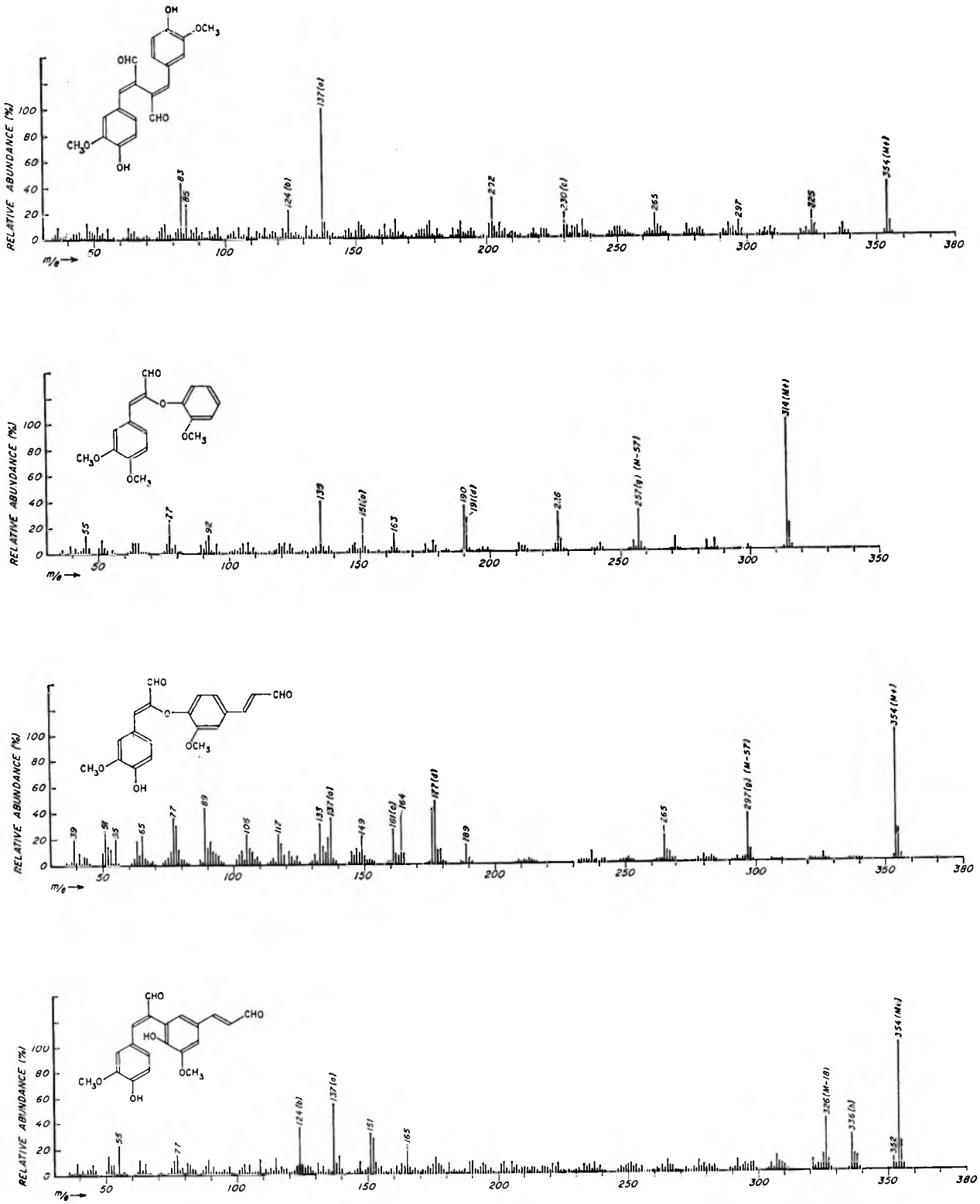
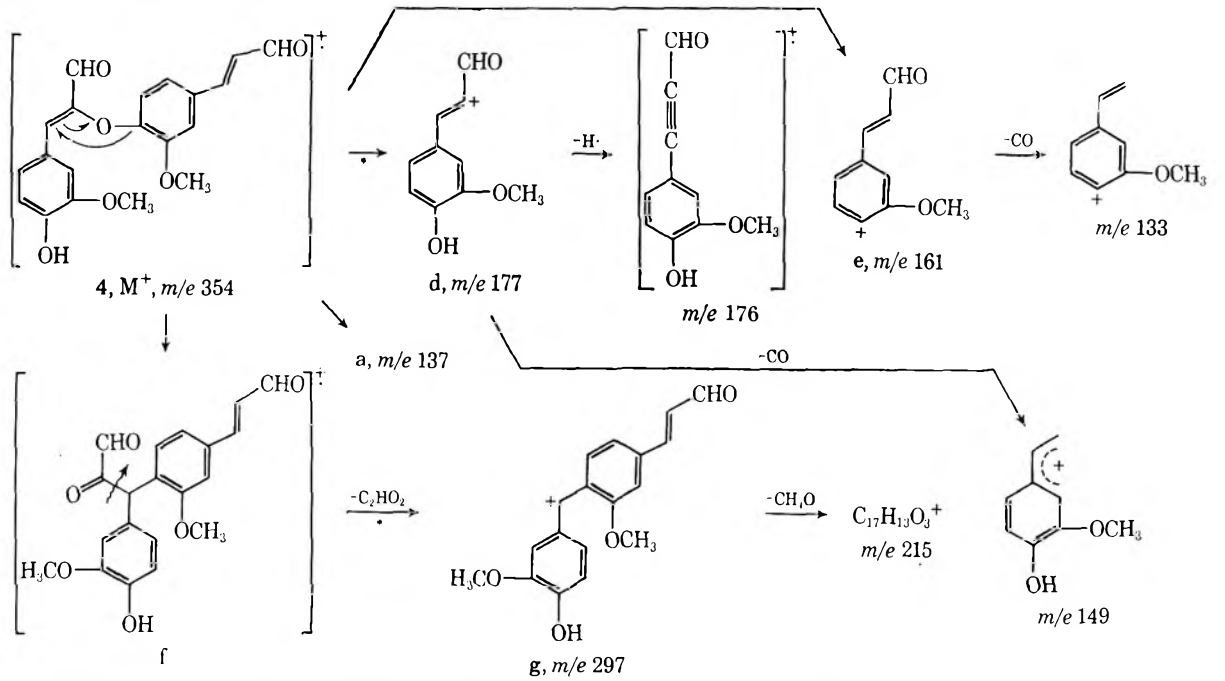


Figure 1.—Mass spectra (from top to bottom) of compounds **3**, **14**, **4**, and **5**.

give the ion at *m/e* 297 (g), as indicated by a metastable peak at *m/e* 249.2. This could be rationalized by assuming 1,3 rearrangement of aryl group to form intermediate f which would give the ion g by the expulsion of HCO–C(O)–. To ensure this, the mass spectrum of α-(2-methoxyphenoxy)coniferaldehyde methyl ether (**14**) was examined (Figure 1). It also exhibited the M − 57 ion peak, which followed the same fragmentation patterns as **4**. The M − 57 ion had thus furnished a further proof of the 2-aroxy-3-arylpropenal skeleton of **4**.

The nmr spectrum of **5** also showed the presence of ArCH=$\overset{|}{\text{C}}$CHO and ArCH=CHCHO. With **5** as with **3**, the vinyl proton singlet was distinguishable and was at δ 7.56. After D_2O exchange, the molecular ion increased by 2 mass units, and there was also an equivalent increase in the M + 1 ion which was attributed to the two possiflle monodeuterated forms of the molecular ion. The M + 2:M + 1:M ratio was 44:42:14, and the overall D_2O exchange ratio was calculated to be 45%. The ion akin to h after D_2O treatment showed

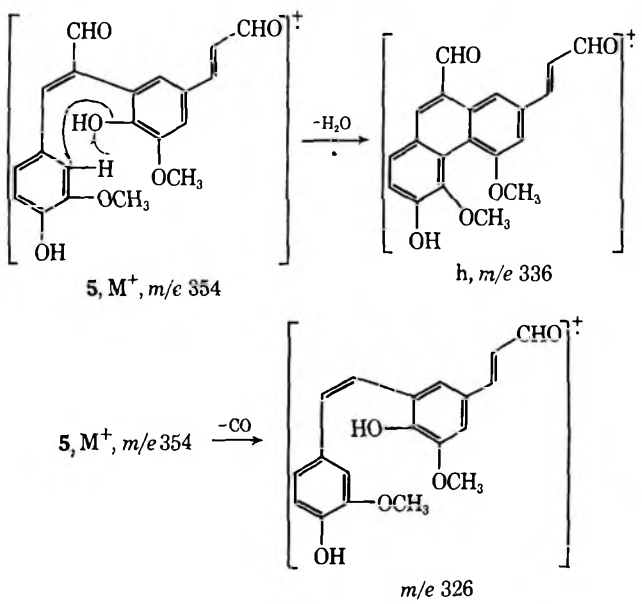
SCHEME II[a]



[a] Transitions substantiated by an appropriate metastable peak are indicated by an asterisk.

prominent peaks at 336 and 337 due to loss of H_2O and HDO from the hydroxyl groups of the molecular ions. The presence of a prominent 338 peak indicates that the water could also be lost from the carboxyl.[12] These were indicative of β-(C-5) linkage, and the structure **5** for the compound was apparent. The mass spectrum (Figure 1, Scheme III) exhibited ion peaks corresponding to M − 18 and M − 28. 1,6 elimination of water from the molecular ion to form the stable anthracene ion (h) was compatible with the structure proposed for the compound.

SCHEME III[a]



[a] Transition substantiated by an appropriate metastable peak is indicated by an asterisk.

Experimental Section

trans-**Coniferaldehyde** (1) was prepared by the method of Pauly[13] and recrystallized from aqueous alcohol: mp 80–82° (lit.[13] mp 82.5°); nmr $CDCl_3$ δ 3.8 (s, 3, OCH_3), 6.55 (m, 1, J = 15.8 Hz, J = 7.8 Hz, CH=CHCHO), 7.0 (m, 3, aromatic), 7.39 (d, 1, J = 15.8 Hz, CH=CHCHO), 9.25 (d, 1, J = 7.8 Hz, CHO).

Dehydrogenation of 1 and Isolation of Dehydro Dimers.—1 (1 g, 0.0056 mol) was dissolved in 1 l. of H_2O with warming, and the solution was cooled to 3° in an ice bath. Horseradish peroxidase[14] (5 mg) was dissolved in a few milliliters of H_2O and added to the solution; then 9.5 ml (0.0056 equiv) of 1% H_2O_2 was added over 30 min while the solution was stirred. Stirring was continued for an additional hour; the mixture was then extracted with EtOAc and residual 1; and the dimeric compounds **3**, **4**, and **5** were isolated by column chromatography on silicic acid with benzene and benzene–EtOH 100:1 solvents. The compounds were purified by preparative tlc on silica gel with benzene–EtOH 100:5 solvent.

2,3-Diformyl-1,4-di-5-guaiacylbuta-1,3-diene (**3**) was crystallized from aqueous EtOH: mp 178–180°; uv max 343 mμ (ε 3.88 × 10⁴), showed a characteristic bathochromic shift to 396 mμ on the addition of 1 drop of 50% NaOH; ir (KBr) 3400 (OH), 1680 (conjugated C=O), 1640 sh, 1595 (C=C), 1520 cm^{-1} (aromatic); nmr (d_6-acetone) δ 3.68 (s, 6, OCH_3), 6.81 (d, 2, J = 8.2 Hz, aromatic), 7.21 (m, 2, J = 8.2 Hz, J = 2 Hz, aromatic), 7.27 (d, 2, J = 2 Hz, aromatic), 7.77 (s, 2, olefinic), 9.66 (s, 2, –CHO); mol wt 354 (mass spectrum).

Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.91; H, 4.99.

α-(4-β-Formylvinyl-2-methoxyphenoxy)coniferaldehyde (**4**) was crystallized from aqueous alcohol: mp 87–89°; uv max 345 mμ (ε 3.8 × 10⁴), showed a characteristic bathochromic shift to uv max 421 mμ on addition of 1 drop of 50% NaOH (a second uv max at 334 nm indicates etherified coniferaldehyde moiety); ir (KBr) 3410 (OH), 1675–1655 (conjugated C=O), 1620, 1600 (C=C), 1515 cm^{-1} (aromatic); nmr $(CDCl)_3$ δ 3.78 (s, 3, OCH_3), 3.95 (s, 3, OCH_3), 6.60 (m, 1, J = 15.8 Hz, J = 7.8 Hz, CH=CH=CHCHO), 7.37 (d, 1, J = 15.8 Hz, CH=CHCHO), 9.65 (d, 1, J = 7.8 Hz, CHO), 9.44 (s, 1, CHO) (the remaining portion of the spectrum could not be interpreted); mol wt 354 (mass spectrum).

Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.65; H, 5.25.

α-(5-β-Formylvinyl-2-hydroxy-3-methoxyphenyl)coniferaldehyde (**5**) was crystallized from aqueous EtOH: mp 191–193°;

(12) J. H. Bowie and P. Y. White, *J. Chem. Soc., B*, 89 (1969).

(13) H. Pauly and K. Feuerstein, *Ber.*, **62B**, 297 (1929).

(14) Peroxidase (horseradish), type I activity approximately 72 purpurogallin units/mg. Purchased from Sigma Chemical Co., St. Louis, Mo.

uv max 339 mμ (ε 3.8 × 10⁴), which showed a characteristic bathochromic shift to uv max 404 mμ on the addition of 1 drop of 50% NaOH; ir (KBr) 3410 (OH), 1670 (conjugated, C=O), 1610, 1600 (C=C), 1520 cm⁻¹ (aromatic); nmr (d_6-acetone) δ 3.52 (s, 3, OCH_3), 4.01 (s, 3, OCH_3), 6.69 (m, 1, J = 7.8 Hz, J = 15.4 Hz, CH=CHCHO), 7.56 (s, 1, CH=CCHO), 7.58 (d, 1, J = 15.4 Hz, CH=CHCHO), 9.57 (d, 1, J = 7.8 Hz, CHO), 9.65 (s, 1, CHO); mol wt 354 (mass spectrum).

Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 68.02; H, 5.08.

α-(2-Methoxyphenoxy)coniferaldehyde Methyl Ether (14).—14 was synthesized by the condensation of veratraldehyde, which is commercially available, and 2-methoxyphenoxyacetaldehyde (15) using the method described[13] for the synthesis of 1: uv max 339 mμ (ε 2.36 × 10⁴), unchanged by the addition of 1 drop of 50% sodium hydroxide; ir (KBr) 1685 (conjugated C=O), 1625, 1600 (C=C), 1515, 1505 cm⁻¹ (aromatic); nmr ($CDCl_3$), δ 3.75 (s, 1, OCH_3), 3.81 (s, 1, OCH_3), 3.91 (s, 1, OCH_3), 9.43 (s, 1, CHO), and a complex aromatic region which was not interpreted; mol wt 314 (mass spectrum).

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found: C, 68.75; H, 5.57.

2-Methoxyphenoxyacetaldehyde (15).—This compound was synthesized by the $Pb(OAc)_4$ oxidation of guaiacol glyceryl ether, which is available commercially, following a previously reported procedure,[15] and the compound was crystallized from benzene, mp 72–74°.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.02. Found: C, 65.16; H, 6.18.

Registry No.—1, 20649-42-7; 3, 24058-19-3; 4, 24058-20-6; 5, 24058-21-7; 14, 24058-22-8.

(15) R. J. Speer and H. R. Mahler, *J. Amer. Chem. Soc.*, **71**, 1133 (1949).

Synthesis of *cis*- and *trans*-4-Mercapto-L-proline Derivatives

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Received October 16, 1969

Both *cis*- and *trans*-N,O-ditosyl-4-hydroxy-L-proline methyl esters under special precautions underwent almost complete SN2 displacements by potassium thiobenzoate to 4-benzoylmercaptoprolines, which were cleaved by dilute methoxide to the autoxidizable (and in the *cis* series lactonizable) N-tosyl-4-mercaptoprolines, easily alkylatable to the N-tosyl-*p*-methoxybenzylmercaptoprolines. These were electrolytically detosylated and converted to N-*t*-butylcarbonyl-*cis*- and -*trans*-4-*p*-methoxybenzylmercapto-L-prolines suitable for incorporation into oligopeptides by the conventional or the solid-phase method.

Although many analogs and homologs of proline and hydroxyproline have been reported,[1,2] the sulfur-substituted prolines[3,4] have not received much attention. For the synthesis of inhibitors of proline hydroxylase,[5] we needed sulfur analogs of natural and *allo*-4-hydroxy-L-proline suitably protected for incorporation into synthetic polypeptides.

The synthesis of such mercaptoprolines becomes an exercise in the proper sequence of putting on and taking off protecting groups with sufficient lability and differential activity to permit these steps to be selective.

The requirement for the S-protecting group of the resulting *cis*- and *trans*-4-mercapto-L-proline peptides was easy removal to liberate sulfhydryl without cleavage of peptide bonds. We chose *p*-methoxybenzyl, which is easily removed from S-protected cysteine peptides by anhydrous hydrogen fluoride.[6,7]

The starting material for the *cis*-mercapto series was N,O-ditosylhydroxy-L-proline methyl ester (I) (Scheme I).[8,9] Analogously the *trans*-mercapto series started with N,O-ditosyl-*allo*-hydroxy-L-proline methyl ester (II) (Scheme II).[2,8]

N-Tosyl-*cis*-4-benzoylmercapto-L-proline methyl ester (III) was prepared from I and potassium thiobenzoate following procedures similar to those developed for conversion of serines to cysteines.[10] The proline reactions are slower and proceed with inversion of configuration requiring additional precautions. When the *trans* → *cis* inversion reaction is run for 6–10 days at a temperature not exceeding 35–40°, the conversion is essentially stereoselective, in contrast to the reaction in refluxing methanol for 20 hr which gave a poor yield of III along with a substantial quantity of N-tosyl-*trans*-4-benzoylmercapto-L-proline methyl ester (IV). The presence of *trans* products in similar displacements on *trans*-4-tosylhydroxy-L-proline methyl ester has been explained by intramolecular participation of the ester carbonyl to form a cyclic carbonium intermediate which favors SN1 substitutions.[11] However, the corresponding *cis* → *trans* inversion to N-tosyl-*trans*-4-benzoylmercapto-L-proline methyl ester (IV) at 35–40° for 6 days also gave a small quantity of the *cis* epimer. The *cis* product probably arose by solvolysis of the *trans*-tosylate with subsequent attack by S-benzoyl anion in a normal SN1 reaction. Thin layer chromatography showed the product resulting from inversion to be major and retention to be the minor pathway.

In analogy to S-benzoyl derivatives of cysteine, sodium alkoxides[12,13] easily cleaved the benzoylthioprolines. With 0.5 *M* methanolic sodium hy-

(1) A. B. Mauger and B. Witkop, *Chem. Rev.*, **66**, 47 (1966).
(2) R. H. Andreatta, V. Nair, A. V. Robertson, and W. R. J. Simpson, *Aust. J. Chem.*, **20**, 1493 (1967).
(3) A. A. Patchett and B. Witkop, *J. Amer. Chem. Soc.*, **79**, 185 (1957).
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(8) Y. Fujita, A. Gottlieb, B. Peterkofsky, S. Udenfriend, and B. Witkop, *J. Amer. Chem. Soc.*, **86**, 4709 (1964).
(9) P. S. Portoghese and A. A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966).
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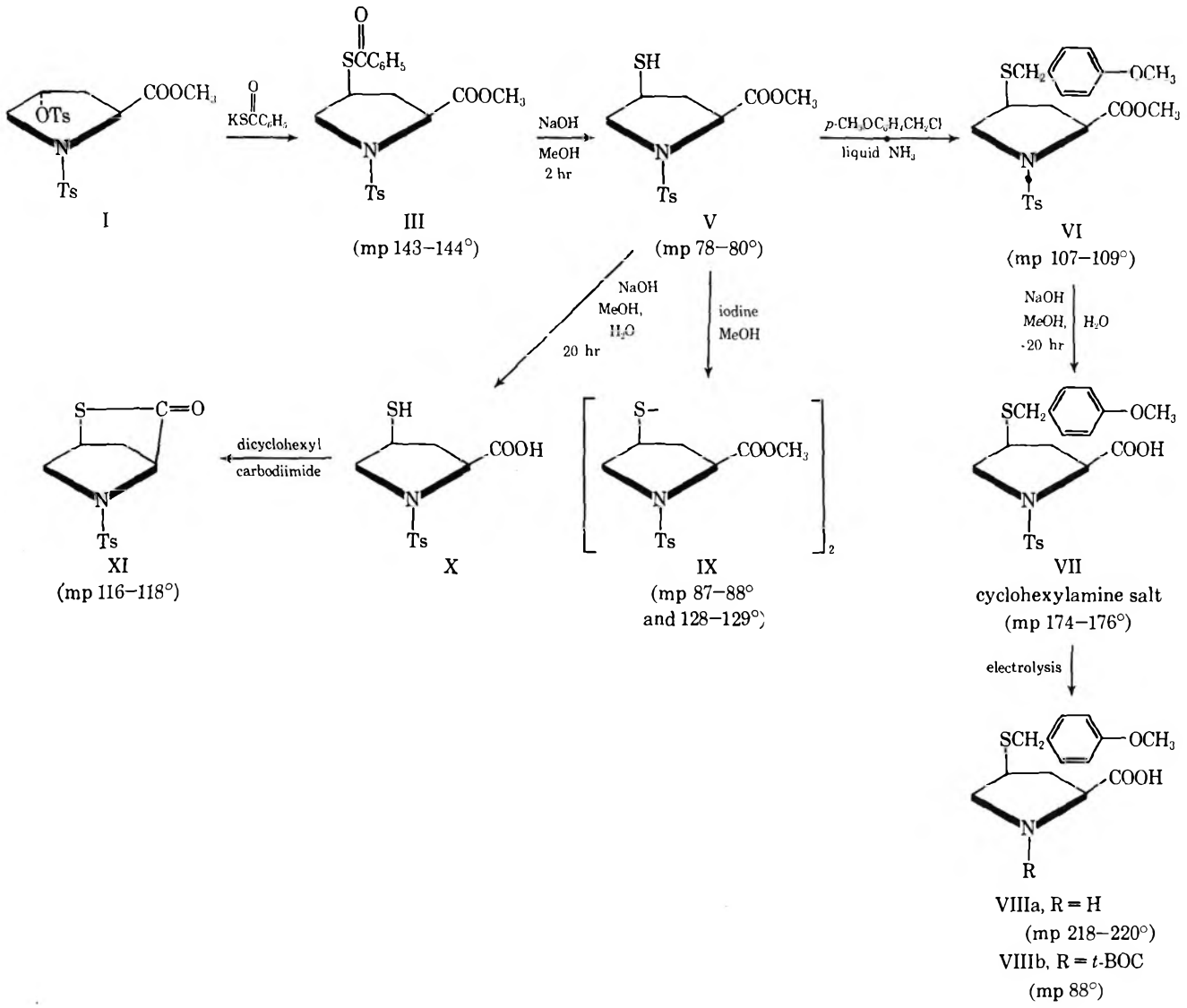
(13) R. G. Hiskey, T. Mizoguchi, and H. Igeta, *J. Org. Chem.*, **31**, 1188 (1966).

SCHEME I



droxide at room temperature, benzoylthioprolines were selectively split in preference to the methyl esters. The resulting N-tosyl-*cis*-4-mercapto-L-proline methyl ester (V) and the *trans* epimer XII are highly sensitive to air oxidation to form the stable crystalline disulfides IX and XVI, which are also easily prepared by oxidation of the mercaptans with iodine in methanol.

In analogy to procedures developed for the cysteines[6] the free thiol groups were protected by *p*-(chloromethyl)anisole in liquid ammonia[14] in good yield. Hydrolysis of the methyl esters gave the corresponding N-tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline (VII) and the *trans* epimer XIV which were easily crystallized and purified as the cyclohexylamine salts.

A variety of methods are available for the cleavage of sulfonamides, many of which are rather drastic.[15] Although prolines have been detosylated by 45% hydrogen bromide in acetic acid, opening of the proline ring has been reported, and several attempts with this reagent were unsuccessful. Electrolytic reductive detosylation[16] proved to be the method of choice. Advantages of the method are low temperature, pure products, ease of separation from the split group, and resistance of the formyl, carbobenzyloxy, and benzylmercapto groups to normal reductive electrolysis. With all of these advantages 80–90% yields of the *cis*- and *trans*-*p*-methoxybenzylmercapto-L-prolines were obtained. The two mercaptoprolines VIIIa and XVa were converted to the *t*-butyloxycarbonyl(*t*-BOC) derivatives VIIIb and XVb which are readily usable for incorporation into peptides by conventional or Merrifield methods.

Lactonization of N-tosyl-*cis*-4-mercaptoproline X to the well-crystallized XI was easily brought about by dicyclohexylcarbodiimide reagent. Thiolactone XI is analogous to N-acetyl lactone[4] in which the absolute configuration at C-4 is *S*.[17]

Experimental Section

All melting points are corrected. Thin layer chromatograms were done on Merck silica gel G with detection by iodine vapor. Solvent systems were (1) methanol; (2) benzene–methanol, 40:1; (3) 1-butanol–pyridine–acetic acid–water, 4:1:1:2; (4) 2-propanol. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind.

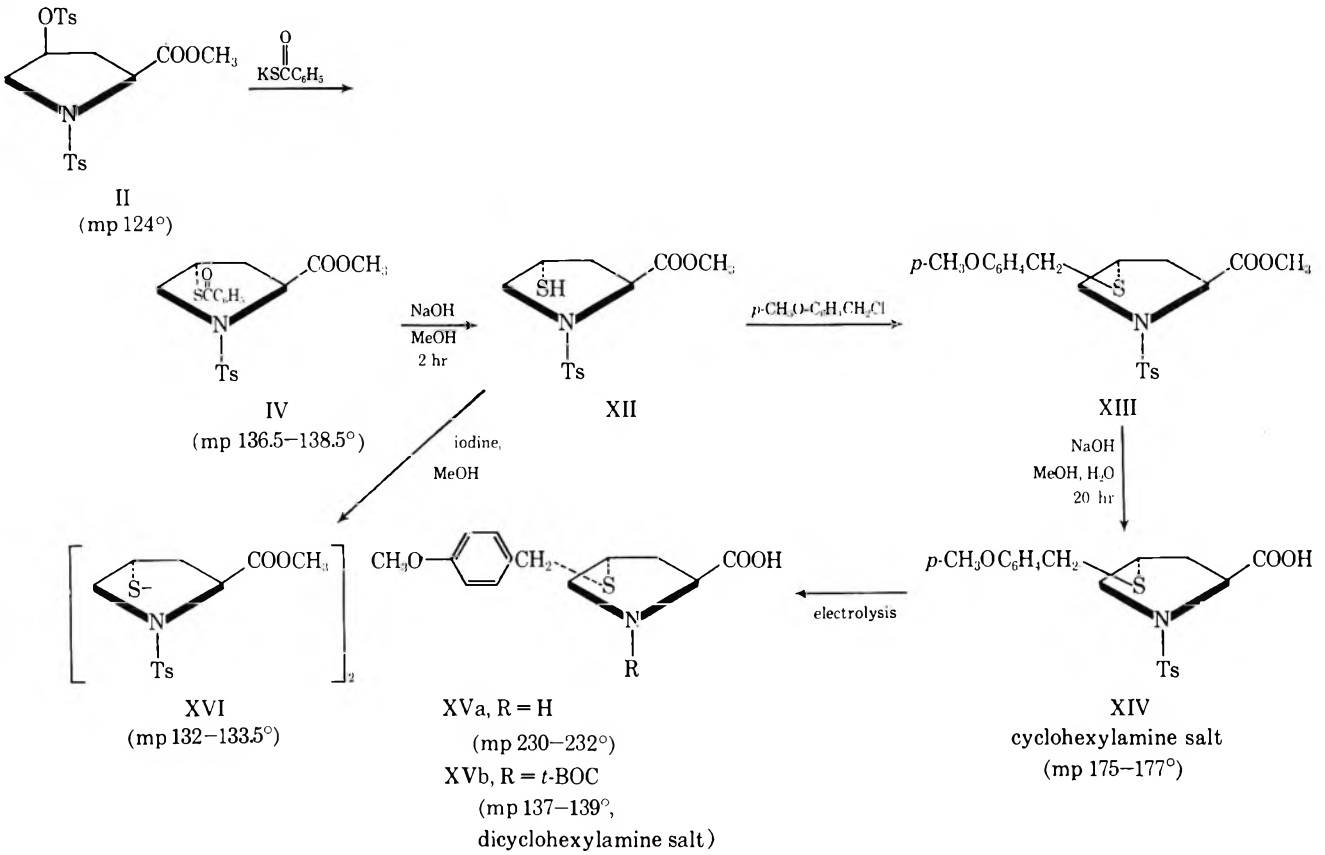
(14) Eastman Kodak No. 3406. This commercial product is stabilized with sodium carbonate but is still dangerous. A 25-g bottle about two-thirds full exploded on the shelf after standing closed for several months.

(15) S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959).

(16) L. Horner and H. Neumann, *Chem. Ber.*, **98**, 1715, 3462 (1965).

(17) *Cf.* B. Witkop, *Chem. Soc., Spec. Publ.*, No. 3, 60 (1955).

SCHEME II



N-Tosyl-*cis*-4-benzoylmercapto-L-proline Methyl Ester (III).—A solution of 4.53 g (0.01 *m*) of N,O-ditosyl-4-hydroxy-L-proline methyl ester (I) and 8.9 g (0.05 *m*) of potassium thiobenzoate in 60 ml of anhydrous methanol was stirred magnetically, and the temperature was kept at 35–40°. A precipitate gradually formed and progress of the reaction was followed by tlc in solvent system 2. After 10 days there was little starting material left. The mixture was cooled; the solid was collected and washed with water, then methanol, to give 2.70 g (68%) of a crude *cis* product, mp 136.5–141°. Tlc indicated contamination by a trace of the *trans*-4-benzoylmercapto isomer. Recrystallization from a mixture of ethyl acetate and ether gave 2.26 g (54%) of orange needles, mp 142.5–144.5°. The compound crystallized well from methanol as orange plates.

Anal. Calcd for $C_{20}H_{21}NO_5S_2$: C, 57.26; H, 5.04; N, 3.34. Found: C, 57.20; H, 5.60; N, 3.41.

N-Tosyl-*trans*-4-benzoylmercapto-L-proline Methyl Ester (IV).—The analogous displacement on II for 6 days at 35–40° eventually yielded 55% crystals, mp 132–135°. Tlc in solvent system 2 showed this product to contain a small amount of the *cis* epimer. Several recrystallizations from ethanol or ethyl acetate–ether gave pink rhomboids, mp 136.5–138.5°.

Anal. Calcd for $C_{20}H_{21}NO_5S_2$: C, 57.26; H, 5.04; S, 15.26. Found: C, 57.17; H, 5.13; S, 15.72.

When this reaction was run on a 10-g scale for 10 days the yield was lower. Also, when the temperature was raised to 50° for 6 days tlc indicated that a variety of other products formed. The main product then became difficult to separate and purify. In one 6-day run at 35° with no warming, 78% of unreacted II was recovered.

N-Tosyl-*cis*-4-mercapto-L-proline Methyl Ester (V).—To a suspension of 5.23 g (0.0125 *m*) of N-tosyl-*cis*-4-benzoylmercapto-L-proline methyl ester (III) in 220 ml of anhydrous methanol under hydrogen was added 30 ml of 0.5 *M* methanolic sodium hydroxide. The reactant dissolved completely after a short time of stirring. After 2 hr, 2 ml of water was added and stirring was continued for 0.5 hr. Neutralization with methanolic hydrochloric acid and evaporation of the solvent left a solid which was extracted into 20 ml of water and 120 ml of ethyl acetate. The organic phase was washed with 10-ml portions of water, 5% sodium bicarbonate, and water again, and then dried over sodium sulfate. Evaporation gave a product which crystallized from carbon tetrachloride–petroleum ether to yield 3.36 g (85%) of colorless crystals, mp 75–80°. Tlc of this crude product in solvent system 2 indicated the presence of a small quantity of the disulfide, which is more slowly detected by iodine than the –SH compound. Recrystallization gave a pure product, mp 78–80°, as a colorless microcrystalline powder.

Anal. Calcd for $C_{13}H_{17}NO_4S_2$: C, 49.52; H, 5.43; S, 20.30. Found: C, 49.65; H, 5.55; S, 20.54.

N-Tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline Methyl Ester (VI).—A mixture of 3.50 g (0.011 *m*) of N-tosyl-*cis*-4-mercapto-L-proline methyl ester (V) and 2.85 g (0.0182 *m*) of *p*-(chloromethyl)anisole in an ice–alcohol cooled flask was treated with 80 ml of liquid ammonia. A colorless precipitate formed immediately and stirring was continued for 0.5 hr with cooling and then at room temperature as excess ammonia evaporated. The crystalline product was washed with water until neutral. One recrystallization of the crude product from carbon tetrachloride yielded 4.28 g (89%) of a powder, mp 99–106°. An analytical sample was recrystallized to colorless fluffy crystals of VI, mp 108–110°.

Anal. Calcd for $C_{21}H_{25}NO_5S_2$: C, 57.92; H, 5.79; S, 14.70. Found: C, 57.47; H, 5.95; S, 15.06.

N-Tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline (VII).—A suspension of 800 mg (1.9 mmol) of N-tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline methyl ester (VI) in 8 ml of 0.5 *M* methanolic sodium hydroxide, 10 ml of methanol, and 10 drops of water was stirred for 20 hr at room temperature. The resulting clear solution was evaporated to dryness, and the solid was taken up in water. Acidification with citric acid gave a precipitate which was extracted into ether and dried over sodium sulfate. Addition of a solution of 220 mg (2.2 mmol) of cyclohexylamine in acetonitrile to the filtered ether solution caused 880 mg of a colorless powder, mp 158–179°, to precipitate. Recrystallization from acetonitrile gave 660 mg (67%) of colorless needles, the cyclohexylammonium salt of VII, mp 175–177°, homogeneous on tlc in solvent system 1.

Anal. Calcd for $C_{20}H_{23}NS_2O_5 \cdot C_6H_{11}NH_2$: C, 59.97; H, 6.97; S, 12.31. Found: C, 59.55; H, 7.25; S, 11.72.

N-Tosyl-*cis*-4-mercapto-L-proline Lactone (XI).—A suspension of 150 mg of N-tosyl-*cis*-4-mercapto-L-proline methyl ester (VI) in 2 ml of 0.5 *M* methanolic sodium hydroxide containing 3 drops of water was allowed to stand at room temperatures for 20

hr under hydrogen. The resulting solution was evaporated to dryness and the residue was taken up in 3 ml of water. Acidification with citric acid released the sulfhydryl compound X which was salted out, extracted into methylene chloride, and dried over magnesium sulfate. A solution of 120 mg of dicyclohexylcarbodiimide in methylene chloride was added, and the reaction mixture was allowed to stand overnight. Evaporation of the solvent left a colorless solid. The lactone was extracted into ethyl acetate leaving behind pure dicyclohexylurea, more of which precipitated upon adding petroleum ether. The mother liquor was treated with Nuchar C190 N and evaporated to a colorless solid, 70 mg, mp 98–112°. Recrystallization from carbon tetrachloride gave fine crystals of lactone XI, mp 116–118°.

Anal. Calcd for $C_{12}H_{13}S_2NO_3$: C, 50.85; H, 4.62; S, 22.63. Found: C, 51.22; H, 4.87; S, 22.34.

Disulfide of N-Tosyl-*cis*-4-mercapto-L-proline Methyl Ester (IX).—A solution of 90 mg (0.3 mmol) of N-tosyl-*cis*-4-mercapto-L-proline methyl ester (V) in 10 ml of methanol was treated dropwise with a 0.1 *N* solution of iodine in methanol until the color persisted. A few drops of concentrated sodium bisulfite solution were added to reduce excess iodine. The solvent was evaporated, and the resulting solid was washed with water, a small amount of methanol, and then ether to give 80 mg of product. Recrystallization from benzene gave colorless fluffy crystals, mp 95–125°, which after cooling and resolidifying had mp 128–129°. Slow recrystallization from dilute solutions in 2-propanol gave the low-melting modification as long needles, mp 87–88°. The product was homogeneous in solvent systems 1, 2, and 4. In system 4 it shows R_f 0.70.

Anal. Calcd for $(C_{13}H_{16}NO_4S_2)_2$: C, 49.66; H, 5.13; S, 20.40. Found: C, 49.41; H, 5.32; S, 20.55.

N-Tosyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline (XIV).—In analogy to the sequence III → V → VI → VII, N-tosyl-*trans*-4-benzoylmercapto-L-proline methyl ester (IV) was converted into the highly sensitive XII which was alkylated with *p*-(chloromethyl)anisole[14] in liquid ammonia. The resulting oily N-tosyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline methyl ester (XIII) was saponified to the acid XIV, a yellow oil which was dissolved in ethyl ether and dried over sodium sulfate. The filtered ether solution was treated with a solution of cyclohexylamine in 15 ml of acetonitrile. The cyclohexylamine salt, mp 171–173°, was recrystallized from an 80-ml portion of acetonitrile containing a few drops of cyclohexylamine to give matted colorless needles, mp 173–176°, homogeneous on tlc in solvent system 1.

Anal. Calcd for $C_{20}H_{23}NS_2O_5 \cdot C_6H_{11}NH_2$: C, 59.97; H, 6.97; S, 12.31. Found: C, 60.01; H, 6.89; S, 12.56.

Disulfide (XVI) of N-Tosyl-*trans*-4-mercapto-L-proline Methyl Ester.—Alkaline hydrolysis in methanolic sodium hydroxide and oxidation of the thiol XII by dropwise addition of 0.1 *M* methanolic iodine gave the disulfide XVI which was recrystallized from carbon tetrachloride–petroleum ether to give an 80% yield of fine colorless needles, mp 132–135°.

Anal. Calcd for $(C_{13}H_{16}NS_2O_4)_2$: C, 49.66; H, 5.13; S, 20.40. Found: C, 49.38; H, 5.15; S, 20.66.

***cis*-4-*p*-Methoxybenzylmercapto-L-proline (VIIIa).**—A solution of 1.1 g (2.1 mmol) of N-tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline (VII) cyclohexylamine salt in 30 ml of 0.85 *M* methanolic tetramethylammonium chloride was poured into a beaker containing a Teflon-coated magnetic stirring bar, a platinum electrode probe immersed in mercury as the cathode, and an RA-84 grade Alundum thimble containing a carbon anode and 3 ml of water as the anolyte. A current of 1 A at 20 V was applied while stirring. The current was maintained at 1 A for 20 min for a total of 1200 C (theoretical requirement 404 C). During this time the applied potential dropped to 10 V, and hydrogen evolution became vigorous. The reaction was monitored by tlc on microscope slides in solvent system 3. The methanolic supernate was brought to pH 6 with acetic acid and evaporated to a small volume. Following the addition of 6 ml of water and refrigeration, there was collected 450 mg (80%) of needles, mp 210–212° dec, homogeneous on tlc in solvent system 3. Recrystallization from water gave small colorless needles, mp 218–220° dec.

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; S, 12.00. Found: C, 58.69; H, 6.68; S, 12.34.

N-*t*-Butyloxycarbonyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline.—The proline VIIIa was converted in 90% yield to the N-*t*-BOC derivative VIIIb according to published procedure:[18] colorless small needles from ether–petroleum ether; mp 88°; $[\alpha]^{20}D$ −56.3° (*c* 1.0, MeOH); tlc in 1-butanol–acetic acid–water (4:1:2), R_f 0.85.

Anal. Calcd for $C_{18}H_{25}NO_5S$: C, 58.8; H, 6.81; N, 3.82. Found: C, 59.03; H, 6.76; N, 3.90.

***trans*-4-*p*-Methoxybenzylmercapto-L-proline (XVa).**—A solution of 1.5 g (2.85 mmol) of N-tosyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline (XIV) cyclohexylamine salt in 40 ml of 0.85 *M* methanolic tetramethylammonium chloride was electrolyzed at 10–20 V and 1 A as described. The current was maintained at 1 A for 27 min for a total of 1620 C (theoretical: 550 C). Identical monitoring and work-up yielded 680 mg (89%) of crystals, mp 218–228° dec, homogeneous on tlc in solvent system 3. Recrystallization from water gave shiny colorless plates, mp 230–232° dec.

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; S, 12.00. Found: C, 58.47; H, 6.69; S, 12.23.

N-*t*-Butyloxycarbonyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline.—Analogously, the proline XVa was converted to the oily *t*-BOC derivative, which was converted to the dicyclohexylammonium salt which formed microcrystalline powder from ether (87% yield): mp 137–139°; $[\alpha]^{20}D$ −11.5° (*c* 1.09, MeOH); tlc in 1-butanol–acetic acid–water (4:1:2), R_f, 0.9.

Anal. Calcd for $C_{30}H_{48}N_2O_5S$: C, 65.7; H, 8.82; N, 5.11. Found: C, 65.66; H, 8.78; N, 5.11.

Dicyclohexylamine Salt of N-Tosyl-*trans*-4-hydroxy-L-proline.—The dicyclohexylamine salt of N-tosyl-*trans*-4-hydroxy-L-proline (mp 152–154°) was prepared in acetonitrile and recrystallized from the same solvent to form colorless prisms, mp 150–152°, homogeneous on tlc in solvent systems 1, nicely separating the proline and dicyclohexylamine components.

Anal. Calcd for $C_{12}H_{15}NO_5S \cdot (C_6H_{11})_2NH$: N, 6.13. Found: N, 6.05.

The dicyclohexylamine salts of the epimeric N-tosyl-*cis*-4-hydroxy-L-proline did not form a crystalline derivative, nor did the *cis*- or *trans*-N-tosyl-4-*p*-methoxybenzylmercapto-L-proline.

N,O-Ditosyl-*cis*-4-hydroxy-L-proline.—This product appeared in 13% yield in the large-scale monotosylation reaction of *allo*-hydroxy-L-proline as a water-soluble by-product. It was recrystallized from ethanol–water to form colorless plates, mp 188–190°.

Anal. Calcd for $C_{19}H_{21}NO_7S_2$: C, 51.92; H, 4.82; S, 14.59. Found: C, 52.20; H, 4.86; S, 14.71.

Registry No.—III, 23912-23-4; IV, 23912-24-5; V, 23967-33-1; VI, 23912-25-6; VII, 23912-26-7; cyclohexylammonium salt of VII, 23912-27-8; VIII, 23912-28-9; VIIIb, 23912-29-0; IX, 23912-30-3; XI, 23912-31-4; cyclohexylamine salt of XIV, 23912-32-5; XVa, 23912-33-6; XVI, 23967-34-2; N-*t*-butyloxycarbonyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline, 23912-34-7; dicyclohexylamine salt of N-tosyl-*trans*-4-hydroxy-L-proline, 23912-35-8; N,O-ditosyl-*cis*-4-hydroxy-L-proline, 20275-08-5.

Acknowledgment.—We are indebted to Dr. H. Aoyagi for the preparation of the *t*-BOC derivatives.

(18) Z. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967).

The Structure of Tulipinolide and Epitulipinolide. Cytotoxic Sesquiterpenes from *Liriodendron tulipifera* L.[1]

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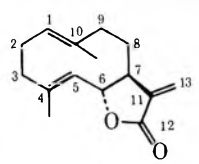
Received October 23, 1969

The structures for two new sesquiterpenes, tulipinolide (**2**) and epitulipinolide (**3**), were shown to be 8α-acetoxy-6(βH),7(αH)-germacra-1(10)-*trans*,4(5)-*trans*,11(13)-trien-6,12-olide and the C-8 epimer, respectively, by cyclization to conformationally rigid decalin products and their study by physical methods. Eupatoriopicrin must be revised to **38** on the basis of yielding degradation products identical with those obtained from epitulipinolide. The application of the α-phenylbutyric anhydride (Horeau) method for establishing the configuration of the hydroxyl at C-8 in deacetylepitulipinolide (**26**), deacetyldihydro-β-cyclotulipinolide (**13**), and deacetyldihydro-β-cycloepitulipinolide (**30**) gave anomalous results, but Brewster's benzoate method yielded values consistent with the configuration assignments made from nmr studies.

We had recently reported the isolation of two cytotoxic substances, costunolide (**1**) and a new sesquiterpene, tulipinolide $C_{17}H_{22}O_4$, mp 181° dec, from *Liriodendron tulipifera* L.[2] Evidence is presented here for the structure of tulipinolide (**2**) and epitulipinolide



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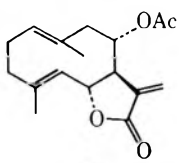
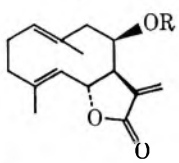
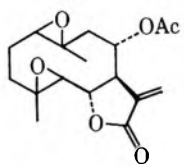


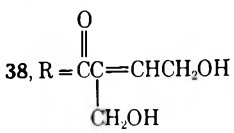
2



3, R = Ac
26, R = H



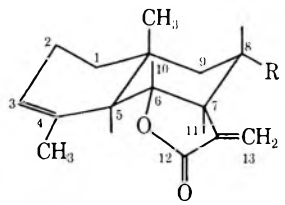
4



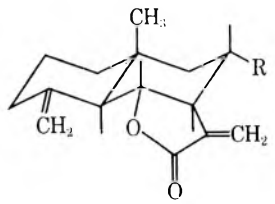
38, R = C(CH$_2$OH)=CHCH$_2$OH

(**3**), a third cytotoxic[3] germacranolide from the same source. The nmr peaks for the substances to be discussed are in Table I.

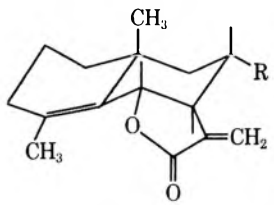
The presence in tulipinolide of an acetate and an α,β'-unsaturated γ-lactone function was previously established.[2] The gross germacranolide structure was indicated by the functional groups as interpreted from the nmr spectrum and supported by the isolation of levulinic acid on ozonolysis and of the diepoxide **4** on peroxidation. Cyclization of tulipinolide (**2**) afforded α-(**5**) and β-cyclotulipinolide (**6**), but surprisingly the γ isomer (**7**) was not detected. These "rigid" decalin compounds allowed the use of nmr to establish their structure and configuration. The stereochemistry at carbons 6, 7, and 8 in the β isomer **6** was determined in this way, for the H_6 proton appears as a triplet at δ 4.07, the X of an ABX pattern ($J_{BX} = J_{BX} = 10.9$ Hz), and the large coupling constants support axial positioning of the H_5, H_6, and H_7 protons. The H_8 proton found at δ 5.23 was placed axial on the basis of the six-peak pattern, the X of an ABMX ($J_{AX} = J_{MX} = 10.7$ and $J_{BX} = 4.5$ Hz) system, the result of interaction of the neighboring two axial and one equatorial protons. The spectral interpretations were aided by comparison with the costunolide cyclized products, α-**8**, β-**9**, and γ-**10**.[4]



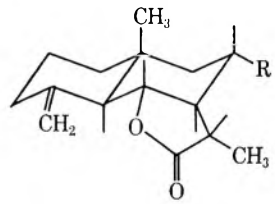
5, R = OAc
8, R = H



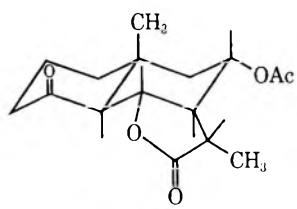
6, R = OAc
9, R = H



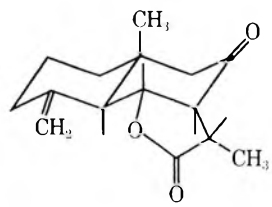
7, R = OAc
10, R = H



11, R = OAc
13, R = H



12



14

The *trans*-decalin system for **6** was established by ozonolysis of dihydro-β-cyclotulipinolide (**11**) to the ketone **12** which exhibited a strong negative Cotton effect peak in the CD at 290 mμ ([θ] −4670), a result predictable from the octant rule.[5] The C_{11} methyl

(1) Antitumor Agents. IV. Previous paper: R. W. Doskotch and C. D. Hufford, *J. Org. Chem.*, **35**, 486 (1970). This investigation was supported by Public Health Service Research Grant No. CA-08133 from the National Cancer Institute and No. FR-03328 from Special Research Resources for purchase of the nmr spectrometer (Varian A-60A) and accessories. Taken in part from the Ph.D. Thesis of F. S. E., June 1969.

(2) R. W. Doskotch and F. S. El-Feraly, *J. Pharm. Sci.*, **58**, 877 (1969).

(3) Tested in the KB cell culture assay through the courtesy of the Cancer Chemotherapy National Service Center (CCNSC) according to the method in *Cancer Chemother. Rep.*, **25**, 22 (1962). Tulipinolide and epitulipinolide showed ED_{50} values of 0.46 and 2.1 μg/ml, respectively.

(4) The α isomer was first obtained crystalline by G. H. Kulkarni, G. R. Kelkar, and S. C. Bhattacharya, *Tetrahedron*, **20**, 2639 (1964), and recently T. C. Jain and J. E. McCloskey, *Tetrahedron Lett.*, 2917 (1969), reported the properties of the β isomer.

(5) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 178. For studies of ketones in the eudesmane series, see D. C. Humber, A. R. Pinder, and S. R. Wallis, *J. Chem. Soc., C*, 2941 (1968).

group in **11** was assigned as α on the basis that the methine proton H_{11} appeared as a six-peak multiplet, the result of the overlap (J = 12.0 Hz) of a pair of quartets (J = 6.7 Hz). In addition, the C_{11} methyl group showed an upfield shift of only 0.09 ppm in deuteriobenzene relative to deuteriochloroform. These two conditions are in accord with observations on other *trans*-fused γ-lactones bearing a pseudoaxial H_{11} proton.[6]

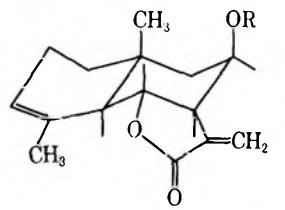
Saponification of dihydro-β-cyclotulipinolide (**11**) produced the alcohol **13**. That no other changes had occurred during hydrolysis was shown by the regeneration of the starting material on reacetylation. Oxidation of the alcohol **13** gave the ketone **14** that gave a negative Cotton effect curve ([θ] −8560 at 290 mμ), as predicted by the use of the octant rule. Other spectral (nmr and ir) features of these derivatives were in agreement with the assignment of the functional groups and their locations in this series.

In repeat collections of plant material tulipinolide was not present; yet the column fraction from which it was originally obtained did not appreciably decrease. The difference was due to the presence of another compound which could not be distinguished from tulipinolide by any number of chromatographic methods yet was separated from it by crystallization from petroleum ether–ethanol mixtures. This new substance, epitulipinolide (**3**), mp 91–92°, [α]D +76°, was shown by the following evidence to be epimeric to tulipinolide at position 8.

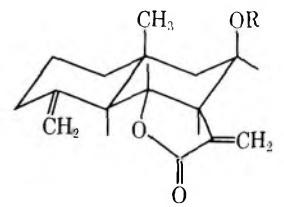
The spectral properties (ir, uv, mass spectrum, and nmr) of epitulipinolide (**3**) were similar to those of tulipinolide. A notable difference was the position of a one-proton multiplet in the nmr at δ 5.72 due to H_8 which in tulipinolide is located between δ 4.8 and 5.2 as part of a four-proton (H_1, H_5, H_6, and H_8) envelope. The corresponding region in the epitulipinolide spectrum was consequently much simplified and now analyzable by first-order methods, the results of which are found in Table I.

Cyclization of epitulipinolide produced the isomers α-(**15**), β-(**16**), and γ-cycloepitulipinolide (**17**), readily characterized by their nmr spectra. The major difference in the spectra between the β isomers of cyclotulipinolide and cycloepitulipinolide occurs for the H_8 multiplet. The six-peak pattern at δ 5.23 in the former is replaced by a four-peak signal at δ 5.71, the X of an ABMX pattern where the three J values are about 3 Hz. This is the consequence of the interaction of an equatorial proton with the neighboring two axial and one equatorial protons. A change in the pattern for the H_7 absorption from a trio of triplets (J values of 2.9, 3.1, 10.7, and 10.9) to a pair of quartets (J values of 3.0, 3.0, 3.3, and 11.0) was a predictable consequence. The downfield chemical shift and the change in coupling constants for H_8 was as anticipated in going from an axial to an equatorial proton.[7]

Hydrogenation of β-cyclopitulipinolide (**16**) afforded the dihydro derivative **18** which on treatment with sodium methoxide gave deacetyldihydro-β-cycloisoepitulipinolide (**19**). That the lactone ring was reclosed to C_8 was evidenced by the sharpening of the ABX triplet (originally the lactonic proton in the starting material **18**) at δ 3.68 (J = 10.5, 10.5 Hz) after treatment with D_2O and formation of dihydro-β-cycloisoepitulipinolide (**20**) on acetylation. In addition, the triplet for the H_6 proton of **19** was lost in forming the oxidation (Moffatt reagent[8]) product **21**.



15, R = Ac
27, R = H



16, R = Ac
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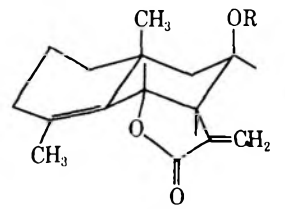
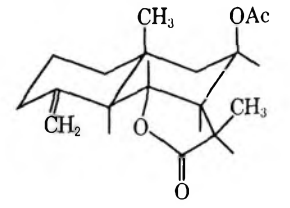
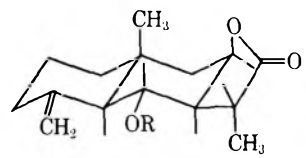


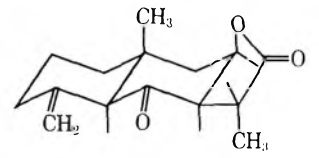
17, R = Ac
29, R = H



18

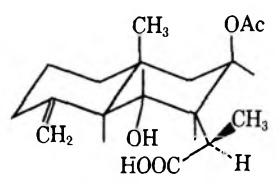


19, R = H
20, R = Ac

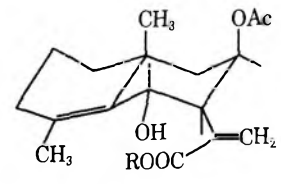


21

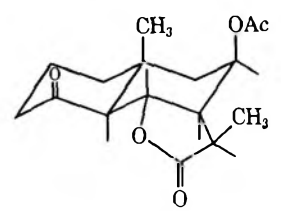
Hydrolysis of **18** under milder conditions (sodium carbonate) easily opened the lactone ring but left the acetate group intact to give the hydroxy acid **22**. A similar lactone opening was possible with γ-cycloepitulipinolide (**17**) to form the hydroxy acid **23**.



22



23, R = H
24, R = CH_3



25

Oxidation of its methyl ester **24** to the corresponding α,β-unsaturated ketone was not successful with man-

(6) C. R. Narayanan and N. K. Venkatasubramanian, *J. Org. Chem.*, **33**, 3156 (1968).

(7) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, Inc., New York, N. Y., 1969, pp 77 and 132.

(8) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965), and references therein.

TABLE I

NMR PEAKS OF COSTUNOLIDE, TULIPINOLIDE, EPITULIPINOLIDE, AND DERIVATIVES[a]

Compound	C_4 —Me or $=CH_2$	C_{10} —Me	H_6	H_7	H_8	C_{11} $=CH_2$ or —Me	Miscellaneous
1	1.70 (br)	1.42 (br)	4.56[b]	2.55 (brm)		5.55 (d, 3.0)	4.85 (brd, 10.0, H_6)
						6.23 (d, 3.5)	
2	1.71 (br)	1.58 (br)		3.08 (brm)		5.84 (dd, 1.5, 3.0)	2.08 ($COCH_3$)
						6.34 (dd, 1.5, 3.5)	4.8–5.2 (H_1, H_5, H_6, and H_8)
3	1.76 (d, 1.3)	1.52 (br)	5.13[c]	2.93 (brm)	5.72 (m)	5.59 (d, 3.1)	2.06 ($COCH_3$)
						6.28 (d, 3.5)	4.78 (dd, 1.3, 10.0, H_6)
4	1.42	1.42	4.6 (m)		4.6 (m)	5.71 (d, 3.0)	2.00 ($COCH_3$)
						6.32 (d, 3.5)	
5	1.87 (br)	0.99	3.98 (dd, 10.8, 11.3)	2.80 (m)	5.30 (m,[d] 4.6, 10.6, 10.7)	5.51 (d, (2.9)	2.13 ($COCH_3$)
						6.11 (d, 3.1)	5.43 (m, H_3)
6	4.85 (br)	0.93	4.07 (dd, 10.9, 10.9)	2.86 (m)	5.23 (m,[d] 4.5, 10.7, 10.7)	5.55 (d, 2.9)	2.13 ($COCH_3$)
	4.99 (br)					6.13 (d, 3.1)	
8	1.85 (br)	0.92	3.88 (dd, 10.0, 11.5)	2.46 (m)		5.38 (d, 3.0)	5.4 (brm, H_3)
						6.05 (d, 3.0)	
9	4.79 (br)	0.85	3.95 (dd, 10.5, 10.5)	~2.6 (m)		5.38 (d, 3.0)	
	4.92 (br)					6.03 (d, 3.2)	
10	1.88 (br)	1.12	4.55 (brd, 11)	2.6 (m)		5.43 (d, 3.0)	
						6.13 (d, 3.3)	
11	4.80 (br)	0.93	4.08 (dd, 10.6, 10.6)		5.15 (m[d] 4.5, 10.6, 10.6)	1.24 (d, 6.7)	2.08 ($COCH_3$)
	4.97 (br)					1.15 (d)[e]	2.59 (dq, 6.7, 12.0, H_{11})
12		0.95	4.18 (dd, 10.6, 10.8)		5.11 (m)[d] 4.6, 10.6, 10.6)	1.23 (d, 6.8)	2.10 ($COCH_3$)
13	4.78 (br)	0.88	4.02 (dd, 10.6, 10.6)		3.98 (m)[f]	1.39 (d, 7)	1.97 (d, 5, OH[g])
	4.96 (br)						2.58 (dq, 7, 12, H_{11})
14	4.88 (br)	0.84	4.15 (dd, 11, 11)			1.28 (d, 6.5)	
	5.04 (br)						
15	1.89 (brd, 1.5)	1.08	4.40 (dd, 11.0, 11.0)	2.80 (m)	5.70 (m)[h]	5.44 (d, 3.1)	2.05 ($COCH_3$)
						6.15 (d, 3.3)	5.42 (br, H_3)
16	4.92 (br)	1.01	4.51 (dd, 11.0, 11.0)	2.88 (m)	5.71 (m)[h]	5.46 (d, 3.0)	2.06 ($COCH_3$)
						6.18 (d, 3.3)	
17	1.90	1.27	5.11 (brd, 12)	2.92 (m)	5.72 (m)[h]	5.51 (d, 3.1)	2.07 ($COCH_3$)
						6.23 (d, 3.4)	
18	5.04 (br)	1.03	4.91 (dd, 11.4, 11.4)		5.65 (m)[h]	1.29 (d, 7.6)	2.11 ($COCH_3$)
	5.15 (br)						2.83 (dq,[i] 7.6, 7.8, H_{11})
19	4.67 (br)	0.88	3.67 (dd, 8.5, 11.0)		4.80 (m,[d] 2.5, 4.5, 4.5)	1.35 (d, 7.5)	2.67 (br, OH[g])
	5.03 (br)						2.93 (q, 7.5, H_{11})
20	4.43	0.91	5.08 (dd, 9.0, 11.4)		4.78 (m,[d] 2.1, 4.8, 4.8)	1.23 (d, 7.6)	2.02 ($COCH_3$)
	4.83						2.9 (q, 7.6, H_{11})
21	5.07 (br)	0.86		2.83 (brd, 6.3)	5.10 (m,[d] 2.5, 4.5, 6.3)	1.31 (d, 7.8)	3.06 (br, H_5)
	5.91 (br)						3.46 (brq, 7.8, H_{11})
22	4.77 (br)	0.87	4.35 (dd, 10.5, 10.5)		5.29 (m)[h]	1.26 (d, 7.3)	1.98 ($COCH_3$)
	5.02 (br)						3.02 (m, H_{11})
							6.70 (br,[g] CH and COOH)
23	1.95 (br)	1.23	5.00 (brd, 11)	3.17 (dd, 4.0, 11.2)	5.17 (m)	5.82 (br)	2.00 ($COCH_3$)
						6.52 (br)	6.67 (br,[g] CH and COOH)
24	1.96 (br)	1.23	5.02 (brd, 11)	3.17 (dd, 4.0, 11.2)	5.15 (m)	5.73 (br)	1.98 ($COCH_3$)
						6.38 (br)	2.1 (br,[g] OH)
							3.78 (OCH_3)
25		1.01	4.82 (dd, 11.0, 11.0)		5.43 (m)[h]	1.21 (d, 7.5)	2.05 ($COCH_3$)
26	1.73 (d, 1.3)	1.63 (br)	5.27 (m)	2.8 (m)	4.6 (m)	5.58 (d, 3.1)	4.6 (m, H_1)
						6.21 (d, 3.5)	
26[j]	1.72 (d, 1.5)	1.69 (d, 1.0)	5.28[k]	2.9 (m)	4.7 (m)	5.65 (d, 3.2)	4.20 (d, 4.5,[g] OH)
							4.7 (m, H_1)
						6.19 (d, 3.5)	4.88 (dd, 1.5, 10.0, H_6)
28	4.88 (br)	1.10	4.58 (dd, 11.1, 11.1)	2.73 (m)	4.60 (m)	5.54 (d, 3.1)	2.23 (br,[g] OH)
	4.96 (br)					6.21 (d, 3.3)	
29	1.88 (br)	1.34	5.20 (brd, 11.4)	2.80 (m)	4.60 (m)	5.55 (d, 3.1)	1.9 (br,[g] OH)
						6.31 (d, 3.4)	
30	4.80 (br)	1.08	4.51 (dd, 10.8, 10.8)		4.28 (m)	1.20 (d, 6.8)	2.38 (br,[g] OH)
	4.91 (br)						2.76 (dq, 6.8, 12.8,[l] H_{11})
31	4.84 (br)	1.00	4.42 (dd, 10.8, 10.8)		5.30 (m)[h]	1.22 (d, 6.7)	2.10 ($COCH_3$)
	4.95 (br)					1.15 (d, 6.8)[e]	2.4 (m, H_{11})
32	5.0 (br, 2H)	1.18	5.22 (brd, 11.2)		5.0 (m)	1.87 (d, 1.8)	2.13 (br,[g] OH)

TABLE I
(*Continued*)

Compound	C_4—Me or $=CH_2$	C_{10}—Me	H_6	H_7	H_8	$C_{11}=CH_2$ or —Me	Miscellaneous
33	5.0 (br, 2H)	1.12	5.1 (brd, 11)		5.90 (dd, 2.2, 4.3)	1.98 (d, 1.9)	2.08 ($COCH_3$)
34	1.70 (d, 1.0)	1.63 (d, 0.5)	5.20[m]		4.35 (m)		2.75 (br,[g] OH)
							3.38 (OCH_3)
							4.72 (dd, 1.5, 10, H_6)
35	1.55 (br)	1.55 (br)					3.33 (OCH_3)
							4.6–5.4 (m, H_1, H_6, H_6)
36	1.58 (br)	1.58 (br)	4.83[n]	4.08 (dt, 2.9, 3.2, 8.0)		5.48 (d, 2.9)	2.89 (d, 10, H_9)
						6.34 (d, 3.2)	3.50 (d, 10, H_9)
							5.15 (brd, 10.5, H_6)
							5.2 (br, H_1)

[a] Spectra were determined as given,[25] with chemical shifts in δ (parts per million) and coupling constants shown in parentheses in hertz; singlets are unmarked, d = doublet, m = multiplet with center given, q = quartet, t = triplet, and br = broadened signal. [b] In the 100-MHz spectrum this proton appears as a pair of doublets of unequal height, the A of an ABX pattern where $J_{AB}/\Delta\nu_{AB}$ = 0.57, J_{AB} = 10.0, and J_{AX} = 8.0. [c] As in *b* but at 60 MHz, $J_{AB}/\Delta\nu_{AB}$ = 0.48, J_{AB} = 10.0, and J_{AX} = 8.1. [d] The multiplet is a split triplet, the X of an ABMX pattern. [e] In C_6D_6 as solvent. [f] Sharpens to a split triplet (J = 4.4, 10.2, and 10.2) after D_2O exchange. [g] Lost in D_2O. [h] A tight "quartet" pattern X of an ABMX where all J values are ~3. [i] A quintet formed by a pair of overlapping quartets stands out clearly in the 100-MHz spectrum. [j] Determined in acetone-d_6 because of greater solubility and more reliable δ and J values. [k] As in *c*, $J_{AB}/\Delta\nu_{AB}$ = 0.42, J_{AB} = 10.0, and J_{AX} = 8.0. [l] Clearly seen as a six-peak pattern in the 100-MHz spectrum. [m] As in *c*, $J_{AB}/\Delta\nu_{AB}$ = 0.35, J_{AB} = 10, and J_{AX} = 9.0. [n] As in *c*, $J_{AB}/\Delta\nu_{AB}$ = 0.35, J_{AB} = 10, and J_{AB} = 9.0.

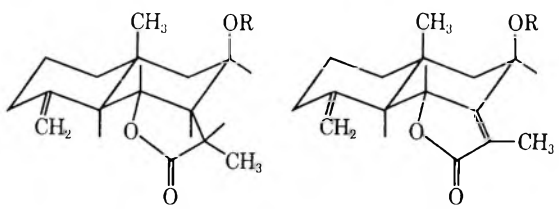
ganese dioxide[9] or Jones,[10] Sarett,[11] or Moffatt reagents.[8] Many reaction products were formed but no ketones were detected (ir). The formation of deacetyldihydro-β-cycloisoepitulipinolide (**19**) from dihydro-β-cycloepitulipinolide was further evidence for placing the C_8 substituent in the axial position, as the resulting *cis*-lactone is more stable than the *trans* isomer.[12]

The stereochemistry at C_{11} was established for deacetyldihydro-β-cycloisoepitulipinolide (**19**) from the presence of a one-proton quartet at δ 2.93 (J = 7.5 Hz) for H_{11}. Double irradiation experiments in which the C_{11} methyl doublet at δ 1.35 was saturated collapsed the quartet to a singlet. Since the coupling constant between H_7 and H_{11} is virtually zero, then H_{11} must be pseudoequatorial in the *cis*-lactone[6] and the C_{11} methyl group is therefore positioned α in **19** and β in dihydro-β-cycloepitulipinolide (**18**).

Dihydro-β-cycloepitulipinolide (**18**) was ozonized to the nor ketone **25** which exhibited, as predicted for a *trans*-decalin system, a negative Cotton effect curve at 290 mμ ([θ] −3870).

Since it was not possible to remove the acetate group from dihydro-β-cycloepitulipinolide (**18**) without changing the position of lactone closing, cyclization of deacetylepitulipinolide (**26**) was necessary if a common product was to be derived from the two tulipinolides. Treatment of epitulipinolide (**3**) with potassium hydroxide yielded the deacetyl compound **26**, mp 186–188°, $[\alpha]^{25}D$ +29.7°. The lactone ring was not altered, for reacetylation gave epitulipinolide. Apparently, the stability difference between *cis*- and *trans*-lactones in the conformationally less rigid germacranolide ring system is not so great as was observed in the eudesmanolide system.

Cyclization of deacetylepitulipinolide (**26**) produced the α-(**27**), β-(**28**), and γ-cyclo-(**29**) isomers of which only the latter two were obtained in pure form. The acetylation of the β isomer **28** yielded β-cycloepitulipinolide (**16**), establishing that the cyclization proceeds in a manner analogous to that for epitulipinolide (**3**). Deacetyl-β-cycloepitulipinolide (**28**) was hydrogenated over palladium-on-charcoal catalyst to give the dihydro compound **30**. The configuration of the newly established asymmetric center (C_{11}) was assigned from the presence of a well-defined sextet for H_{11} in the 100-MHz nmr spectrum and is the same as found for dihydro-β-cyclotulipinolide (**11**). Acetylation of **30** gave compound **31**, the C_{11} epimer of dihydro-β-cycloepitulipinolide (**18**). Apparently, in the hydrogenation the C_8 axial hydroxyl group does not introduce a significant steric hindrance relative to that of the H_8 proton in β-cyclotulipinolide (**6**) to influence the manner of hydrogen transfer, yet an acetate group as in **28** reverses the manner. A minor product of the hydrogenation of **28** was the isomer **32** in which the conjugated exocyclic methylene was converted into a vinyl methyl group. Reexamination of the reduction by-products from β-cycloepitulipinolide (**16**) hydrogenation revealed the presence of the corresponding isomeric acetate **33**. Migration of the double bond in this manner on a catalyst surface has been well established for other unsaturated γ-lactones, especially in the pseudoguaianolide series.[13]



30, R = H
31, R = Ac
32, R = H
33, R = Ac

(9) S. Ball, T. W. Goodwin, and R. A. Morton, *Biochem. J.*, **42**, 516 (1948).

(10) B. Tursch, I. S. deS. Guimaraes, B. Gilbert, R. T. Aplin, A. M. Duffield, and C. Djerassi, *Tetrahedron*, **23**, 761 (1967).

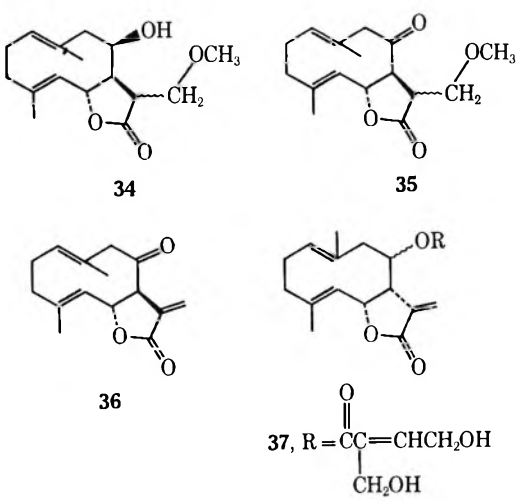
(11) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(12) G. H. Kulkarni, G. E. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 2639 (1964); C. D. Hufford and R. W. Doskotch, unpublished results on studies connected with the *cis*-lactone pseudoguaianolide damsin.

(13) Numerous examples can be found in the review by J. Romo and A. Romo de Vivar, *Progr. Chem. Org. Natur. Prod.*, **25**, 90 (1967).

Oxidation of dihydrodeacetyl-β-cycloepitulipinolide (**30**) with Jones reagent yielded a product identical with the ketone **14** obtained from β-cyclotulipinolide (**6**). It follows that epitulipinolide (**3**) differs from tulipinolide (**2**) in the stereochemistry at C_8 and the only remaining uncertainty in their structures was the stereochemistry of the two endocyclic double bonds. Snatzke and coworkers[14] have studied the CD characteristics of a series of germacranolides and concluded that the "optically active" absorption bands at about 220 and 200 mμ are due to the exciton splitting of the homoconjugated transannular double bonds. These in turn reflect the chirality of that system. Costunolide with two *trans* endocyclic double bonds[15] exhibited a positive Cotton effect curve at 220 mμ ([Θ] +110,000), but the lower wavelength peak was not reached. Tulipinolide and epitulipinolide gave similar results with positive peaks at 221 ([Θ] +121,000) and 222 mμ ([Θ] +146,000), respectively. The two new germacranolides consequently possess two *trans* trisubstituted double bonds.[16] There was also observed in the CD a small negative Cotton effect curve at about 265 mμ for these three compounds. This absorption has been related recently to the stereochemical effect on the $n \rightarrow \pi^*$ transition of the lactone carbonyl.[18] Our assignments are in complete agreement.

With the structures for tulipinolide and epitulipinolide thus established, it was possible to resolve a number of inconsistencies that appeared early in the study. Epitulipinolide (**3**) on hydrolysis with sodium methoxide gave the alcohol **34** which on oxidation afforded the ketone **35**. The conditions of the oxidation were the same as those used to convert deacetylepitulipinolide (**26**) into the corresponding ketone **36**, which showed no major uv absorption peaks above 210 mμ and which gave a positive Zimmerman's test. The three derivatives **26**, **34**, and **35** have physical properties (melting point, specific rotation, and characteristic bands in the ir and uv) like those of substances reported to be derived in a similar manner from eupatoriopicrin (**37**).[19] On the basis of our results the structure for eupatoriopicrin should be revised to **38** and the derivatives thereof changed accordingly.



In order to verify the stereochemical assignment of the acetate group in epitulipinolide by another procedure the Horeau "partial resolution" method[20] was employed and deacetylepitulipinolide (**26**) was esterified with α-phenylbutyric anhydride. The α-phenylbutyric acid isolated after acylation was negative in an optical yield of 39.7%, thus requiring that the C_8 carbon have an *S* configuration. Since the nmr and CD studies supported an *R* configuration, this unexpected result needed explanation. When the Horeau method was applied to deacetyldihydro-β-cyclotulipinolide (**13**) and deacetyldihydro-β-cycloepitulipinolide (**30**) the isolated acid was positive (32.8%) and negative (19.4%), respectively, and requiring again configurations opposite to previous assignments. Application of Brewster's benzoate method,[21] however, did yield results consistent with the initial designations, for the difference in molecular rotation between the benzoate of deacetyldihydro-β-cyclotulipinolide and the carbinol **13** was +176° (suggesting as *S* configuration) and that for the benzoate of deacetyldihydro-β-cycloepitulipinolide and **30** was −195° (suggesting an *R* configuration).

The Horeau method has been applied to a number of natural products[22] including some sesquiterpene lactones of the pseudoguaianolide series.[23] The correct configuration was obtained for these examples where assignment of relative bulk for groups on carbons adjacent to the hydroxyl-bearing carbon was made according to the established order: $R_3C- > R_2CH- > RCH_2-$. In cases where the shape of the entire molecule could influence the shielding of the hydroxyl, the simple rules break down. Examples of such cases have been considered[24] and to these can now be added the eudesmanolide alcohols **13** and **30**. The steric hindrance from the C_{10} methyl, though one methylene group away from the hydroxyl-bearing carbon (C_8), appears to be greater than from the adjacent trisubstituted carbon (C_7). For the more flexible deacetylepitulipinolide (**26**) the answer is less obvious, unless the C_{10} methyl group is considered to be held by a ring conformation in a manner which crowds the hydroxyl group. Studies with deacetyltulipinolide might have contributed to a better understanding of this anomaly, but, unfortunately, the paucity of starting material prevented the development of hydrolysis conditions to yield that product.

(14) G. Snatzke, *Riechs. Aromen, Koerperpflegem.*, **19**, 1 (1969); M. Suchy, L. Dolejs, V. Herout, F. Sorm, G. Snatzke, and J. Himmelreich, *Collect. Czech. Chem. Commun.*, **34**, 229 (1969).

(15) R. B. Bates and D. M. Gale, *J. Amer. Chem. Soc.*, **82**, 5749 (1960).

(16) A substance having the same general structure as tulipinolide [mp 180° dec, $[\alpha]_D$ +249° (*c* 4.8, $CHCl_3$), and identical stereochemistry at C_6, C_7, and C_8] has been proposed for acetoxycostunolide [mp 98°, $[\alpha]_D$ −37.4° (*c* 5.9, $CHCl_3$)], a crystalline acetate of an oily alcohol from *Artemisia balchanorum* H. Krasch.[17] The latter substance most probably differs from tulipinolide in the stereochemistry of the double bonds.

(17) M. Suchy, V. Herout, and F. Sorm, *Collect. Czech Chem. Commun.*, **28**, 1618 (1963).

(18) T. G. Waddell, W. Stocklin, and T. A. Geissman, *Tetrahedron Lett.*, 1313 (1969).

(19) L. Dolejs and V. Herout, *Collect. Czech. Chem. Commun.*, **27**, 2654 (1962).

(20) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(21) J. H. Brewster, *ibid.*, **13**, 106 (1961), and references therein, as well as M. Miyamoto, K. Morita, Y. Kawamatsu, Y. Kawashima, and K. Nakanishi, *ibid.*, **23**, 411 (1967).

(22) References to terpene and steroid examples are given in ref 23. A mold metabolite, caldariomycin, in which the hydroxyl is flanked by α-chloro groups was studied by S. M. Johnson, I. C. Paul, K. L. Rinehart, Jr., and R. Srinivasan, *J. Amer. Chem. Soc.*, **90**, 136 (1968).

(23) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).

(24) A. Marquet and A. Horeau, *Bull. Soc. Chim. Fr.*, 124 (1967).

Experimental Section[25]

Isolation of Tulipinolide (2) and Epitulipinolide (3).—The method for isolating tulipinolide (2), mp 181° dec, $[\alpha]^{28}D$ +260° (*c* 1.0, C_6H_6), $[\alpha]^{25}D$ +249° (*c* 4.8, $CHCl_3$), CD (*c* 0.046 and 0.0023, MeOH), 25°, $[\Theta]_{264}$ −4780, $[\Theta]_{221}$ +121,000, has been reported.[2] Epitulipinolide (3) was obtained in a similar manner from later collections of *Liriodendron tulipifera* L.,[26] and from the mother liquors of tulipinolide by crystallization from petroleum ether (40–60°)–C_2H_5OH. In one collection simply concentrating the petroleum ether percolate at reduced pressure and adding an equal volume of isopropyl ether gave a 0.5% yield of crystalline epitulipinolide (3): mp 91–92°; $[\alpha]^{25}D$ +76° (*c* 3.2, $CHCl_3$); CD (*c* 0.040 and 0.0020, MeOH), 25°, $[\Theta]_{264}$ −7180, $[\Theta]_{222}$ +146,000; uv end absorption 210 mμ (log ε 4.36); ir 1767 and 1673 cm^{-1} (α,β-unsaturated γ-lactone), 1735 and 1250 cm^{-1} (acetate). The mass spectrum showed M^+ 290 (0.1%) and other peaks at *m/e* 248 (1.3), 230 (20), and 43 (100).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.28; H, 7.81.

Epoxidation of Tulipinolide (2).—To 300 mg of *m*-chloroperbenzoic acid in 20 ml of $CHCl_3$ was added 145 mg of **2**. After 24 hr at 5° the solution was shaken with 10-ml portions of 5% aqueous Na_2SO_3 until the $CHCl_3$ layer gave a negative starch-iodide test and then extracted with dilute $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The residue gave 121 mg (absolute C_2H_5OH) of the diepoxide **4**: mp 180–181°; $[\alpha]^{25}D$ +81° (*c* 0.34, CH_3OH); ir 1775 (γ-lactone), 1749, 1240 (acetate), and 1662 cm^{-1} (exocyclic olefin).

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.55; H, 6.82.

Ozonolysis of Tulipinolide (2).—A solution of 290 mg of **2** in 40 ml of ethyl acetate at 0° was treated with 1% ozone in oxygen for 30 min. The residue on evaporation at reduced pressure and 30° was treated with 25 ml of water, warmed for 1 hr on a steam bath, and steam distilled. The distillate collected in 25 ml of 2.5% 2,4-dinitrophenylhydrazine in 2 *N* H_2SO_4 gave 139 mg of an orange-red precipitate which crystallized from chloroform as yellow-orange needles (107 mg), mp 206° which showed no depression when admixed with an authentic sample of the 2,4-dinitrophenylhydrazone of levulinic acid. Both gave the same ir spectrum.

Cyclization of Costunolide (1).—A solution of 250 mg of costunolide (1) {CD (*c* 0.020 and 0.0010, CH_3OH), 25°, $[\Theta]_{262}$ −6660, $[\Theta]_{220}$ + 110,000} in 50 ml $CHCl_3$ containing 0.1 ml of $SOCl_2$[27] was kept at room temperature for 30 min. The oily residue (266 mg) remaining after evaporation of solvent at reduced pressure and 40° showed one spot (R_f 0.6) on tlc (isopropyl ether as solvent). On tlc plates [petroleum ether–isopropyl ether (3:1)] poured with 5% $AgNO_3$,[28] three spots were obtained but better resolved with 15% $AgNO_3$, giving R_f 0.10 [β-cyclocostunolide (**9**)], 0.22 [α-cyclocostunolide (**8**)], and 0.39 [γ-cyclocostunolide (**10**)].

The mixture of cyclocostunolides was applied to a column of 14 gm of silica gel G (15% $AgNO_3$) and elution with the solvent system of petroleum ether–isopropyl ether (3:1) gave 26 mg of a γ-cyclocostunolide fraction which from C_2H_5OH–H_2O yielded **10** as needles: mp 87–88°; $[\alpha]^{25}D$ +22.2° (*c* 0.135, CH_3OH); uv end absorption 210 mμ (log ε 4.43); ir 1765, 1670, 1257, and 825 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 6.86. Found: C, 77.31; H, 8.71.

After the γ-cyclocostunolide was eluted, the solvent was changed to isopropyl ether which gave the α-cyclocostunolide fraction (111 mg). On crystallization from C_2H_5OH–H_2O, **8** was obtained: mp 82–83° $[\alpha]^{25}D$ +112° (*c* 0.25, CH_3OH); uv end absorption 210 mμ (log ε 4.07) {lit.[4] mp 83–84°; $[\alpha]^{25}D$ +118° ($CHCl_3$); uv end absorption 210 mμ (log ε 4.00)}.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.48; H, 8.84.

The β-cyclocostunolide fraction (106 mg) was obtained by continued washing of the column with the same solvent until the effluent no longer contained a $KMnO_4$ reducing solute. Crystallization from C_2H_5OH–H_2O yielded **9**: mp 68–69°; $[\alpha]^{25}D$ +166° (*c* 0.235, CH_3OH); uv end absorptions 210 mμ (log ε 3.89) {lit.[4] mp 66.5–67°; $[\alpha]^{27}D$ +179° ($CHCl_3$); uv end absorption 205 mμ (log ε 4.18)}; ir 1762, 1673, 1651 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.39; H, 8.52.

Cyclization of Tulipinolide (2).—To 534 mg of **2** in 50 ml of chloroform was added 1.0 ml of $SOCl_2$. After 30 min the solvent was evaporated at reduced pressure and the residue crystallized from isopropyl ether to give 239 mg of needles, mp 110–111°, which gave two spots on tlc with 5% $AgNO_3$-impregnated adsorbent. Separation of these crystals was accomplished on a column with 14 g of the same adsorbent using isopropyl ether–$CHCl_3$ (4:1) as solvent. The first eluted material was the α-cyclotulipinolide fraction (49 mg) from which 40 mg of **5** crystallized (isopropyl ether) as prisms: mp 110–111°; $[\alpha]^{25}D$ +187° (*c* 0.685, MeOH); uv end absorption 210 mμ (log ε 4.20); ir 1767 (γ-lactone), 1739 (acetate), 1671 (olefin), and 1200–1255 cm^{-1} (C–O–C stretching).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.33; H, 7.77.

The second eluted fraction (160 mg) crystallized as plates from isopropyl ether to give β-cyclotulipinolide (**6**) (140 mg): mp 136–137°; $[\alpha]^{25}D$ +213° (*c* 0.305, CH_3OH); uv end absorption 210 mμ (log ε 3.83); ir 1767, 1737, 1668, 1645, and 1200–1255 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.43; H, 7.75.

An additional proportionate amount of compounds **5** and **6** could be obtained from the cyclization reaction mother liquors. The presence of γ-cyclotulipinolide was not observed.

Dihydro-β-cyclotulipinolide (11).—β-Cyclotulipinolide (**6**) (81 mg) in 13 ml of absolute C_2H_5OH was hydrogenated over 66 mg of 5% Pd on charcoal at atmospheric pressure and ambient temperature. After uptake (10 min) of 1 mol equiv of hydrogen, the catalyst was removed and the solvent evaporated. The oily residue (82 mg) showed two spots on tlc (isopropyl ether–$CHCl_3$ (4:1)) at R_f 0.55 and 0.40 utilizing $AgNO_3$-treated plates. A column separation utilizing the same adsorbent (14 g) and solvent system gave 20 mg of the first less-polar fraction which was shown by nmr to be a mixture of at least two substances and was not further studied. Decreasing the amount of catalyst by about one-half eliminated this first fraction.

The second fraction (54 mg) on crystallization from isopropyl ether gave pure dihydro-β-cyclotulipinolide (**11**) as plates (40 mg): mp 139–140°; $[\alpha]^{25}D$ +136° (*c* 0.415, CH_3OH); ir 1775 (γ-lactone), 1735 (acetate), and 1648 cm^{-1} (olefin).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.17; H, 8.44.

Ozonolysis of Dihydro-β-cyclotulipinolide (11) to the Ketone 12.—A solution of 50 mg of **11** in 10 ml of acetic acid at 10° was treated with a stream of oxygen containing about 3% ozone for 10 min. The reaction solution at ambient temperature was shaken with 0.25 g of Zn dust for 30 min and then filtered. The residue remaining after evaporation of the solvent was crystallized from isopropyl ether–C_2H_5OH to give 22 mg of the ketone **12**: mp 178–179°; $[\alpha]^{25}D$ +63.7° (*c* 0.245, CH_3OH); CD (*c* 0.105, CH_3OH), 25°, $[\Theta]_{290}$ −4670; uv max 285 mμ (ε 35); ir 1780 (γ-lactone) and 1730 cm^{-1} (a broad double-intensity band for acetate and cyclohexanone) and no olefinic bands.

(25) Melting points were taken in capillaries on a Thomas–Hoover apparatus and are uncorrected. Elemental analyses were by Mr. Joseph F. Alicino, Metuchen, N. J., and by Dr. Alfred Bernhardt, Germany. Infrared spectra were taken in $CHCl_3$ on a Perkin-Elmer Model 237 or 257 spectrophotometer and ultraviolet spectra were obtained in CH_3OH on a Cary Model 15 spectrophotometer. The nmr spectra were measured in $CDCl_3$ on a Varian A-60A instrument with $(CH_3)_4Si$ as internal standard unless otherwise stated, and chemical shifts reported in δ (ppm) units. The ORD, CD, and optical rotation values were determined on a Jasco ORD/UV-5 spectropolarimeter or the latter on a Zeiss polarimeter. Mass spectra were obtained on an AEI MS-9 double-focusing instrument and samples were introduced *via* the direct inlet probe. Thin layer chromatography (tlc) was performed on silica gel G (Merck) with detection by iodine vapor or spraying with 0.3% $KMnO_4$ solution. Plates incorporating $AgNO_3$ were poured as a slurry with the per cent (w/v) of complexing agent indicated. Columns run with such adsorbents were made from thep owdered (through 100-mesh), dried (110°) slurries prepared for the plates and were continuously protected from light.

(26) Collections of root bark were obtained from trees grown in Virginia through the courtesy of Dr. Robert E. Perdue, Jr., of the U. S. Department of Agriculture, Beltsville, Md., under agreement with the CCNSC. The 1964 collection contained 0.4% tulipinolide and 0.1% epitulipinolide, but the 1965 and 1968 supply yielded only epitulipinolide.

(27) The use of thionyl chloride for cyclization is unusual and was discovered accidentally. Its exact role has yet to be determined, but, since the yields obtained with it were better than those from the use of boron trifluoride etherate or hydrochloric acid, it was employed exclusively.

(28) A collection of references to separations of unsaturated substances on $AgNO_3$-treated adsorbents is found in E. Heftmann, "Chromatography," 2nd ed. Reinhold Publishing Corp., New York, N. Y., 1967, pp 485–488.

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 62.59; H, 7.73.

Deacetyldihydro-β-cyclotulipinolide (13).—To a 2.5-ml solution of $NaOCH_3$ from 12 mg of Na was added 60 mg of dihydro-β-cyclotulipinolide (11). After 20 hr at ambient temperature the solution was acidified with acetic acid, diluted with water, and extracted with $CHCl_3$ several times. The $CHCl_3$ extract was washed with water and dried (Na_2SO_4), and the residue after evaporation was crystallized as long needles from isopropyl ether–$CHCl_3$ to give 43 mg of **13**: mp 218–219°; $[\alpha]^{25}D$ +172° (*c* 0.38, CH_3OH), $[M]D$ +432°; ir 3593 and 3443 (hydroxyl), 1765 (γ-lactone), 1650 and 873 cm^{-1} (olefin).

The product **13** was reacetylated by treatment of 20 mg with 0.5 ml each of acetic anhydride and pyridine for 24 hr followed by the usual work-up to give a substance (20 mg) identical (melting point, mixture melting point, and ir) with dihydro-β-cyclotulipinolide **11**.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.31; H, 9.05.

The benzoate ester of **13** was prepared by treatment of 40 mg of **13** with 0.50 ml of pyridine and 0.10 ml of benzoyl chloride for 24 hr; 5 ml of H_2O was then added followed by 100 ml of ether. The reaction mixture was extracted successively with 1 *N* H_2SO_4, H_2O, 5% $NaHCO_3$, and H_2O, then dried (Na_2SO_4). Removal of solvent left 39 mg of an oil that was purified on 7 g of 5% $AgNO_3$-prepared adsorbent, eluting with isopropyl ether–$CHCl_3$ (4:1). The first fraction (22 mg) was crystallized from isopropyl ether–CH_3OH to give 13 mg of the benzoate as needles: mp 106–107°, $[\alpha]^{25}D$ +171.4° (*c* 0.28, CH_3OH), $[M]^{25}D$ +607°. The ir lacked -OH absorption but showed peaks at 1715 (benzoate ester), 1603, and 1583 cm^{-1} (aromatic). The difference in $[M]D$ between the benzoate and the alcohol ($[M]D$ +432°) is +175°, indicating an alcohol with an *S* configuration.[21]

In the Horeau procedure, 96.0 mg of α-phenylbutyric anhydride and 21.0 mg of **13** in 0.8 ml of pyridine were allowed to react for 16 hr. The optically active α-phenylbutyric acid {71.0 mg, $[\alpha]^{25}D$ +4.93° (*c* 1.42, C_6H_6)} was isolated as already described.[23] The optical yield was (+) 32.8% suggesting an *R* configuration for the alcohol. The examination of the neutral fraction by ir showed no starting material.

Oxidation of Deacetyldihydro-β-cyclotulipinolide (13) to the Ketone 14.—Compound **13** (20 mg) in 2 ml of acetone was stirred magnetically and 0.05 ml of Jones reagent[10] was added. After 5 min at ambient temperature, 2 ml of CH_3OH was added followed by 50 ml of diethyl ether. The ether solution was extracted with 1% $NaHCO_3$ and water and then dried (Na_2SO_4). Evaporation of the solvent left an oil that crystallized from isopropyl ether as prisms to give 15 mg of ketone **14**: mp 141–142°; $[\alpha]^{25}D$ −27.3° (*c* 0.128, CH_3OH); CD (*c* 0.128, CH_3OH), 25°, $[\Theta]_{290}$ −8560; uv max 280 mμ (ε 29); ir 1769 (γ-lactone), 1725 (cyclohexanone), 1651, and 875 cm^{-1} (olefin).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 72.55; H, 8.12. Found: C, 72.33; H, 8.02.

Cyclization of Epitulipinolide (3).—A solution of 1.0 g of **3** in 30 ml of chloroform containing 1.0 ml of $SOCl_2$ was kept at ambient temperature for 30 min with occasional stirring. Removal of solvent by evaporation left 1.05 g of an oily residue that crystallized on addition of isopropyl ether to give 680 mg of a mixture of needles and prisms (mp 121–122°). Tlc on 5% $AgNO_3$-impregnated plates [isopropyl ether–$CHCl_3$ (4:1)] revealed three spots, R_f 0.53 [γ-cycloepitulipinolide (**17**)], 0.40 [α-cycloepitulipinolide (**15**)], and 0.15 [β-cycloepitulipinolide (**16**)]. Separation of the isomers was performed on columns using the same solvent system and adsorbent, 14 g for each 200 mg of the mixture (crystalline and mother liquor residue). Typical results are as follows.

The first fraction (tlc-monitored) crystallized from isopropyl ether–C_2H_5OH to give glistening needles (29 mg) of the γ isomer **17**: mp 151–152°; $[\alpha]^{25}D$ −47.0° (*c* 0.50, CH_3OH); uv end absorption 210 mμ (log ε 4.22); ir 1768 (γ-lactone), 1731 (acetate), 1650 (olefin), and 1250 cm^{-1} (C–O–C).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.20; H, 7.40.

The second fraction crystallized slowly from isopropyl ether to give 39 mg of feathery needles of the α isomer **15**: mp 75–76°; $[\alpha]^{25}D$ +45.6° (*c* 0.34, CH_3OH); uv end absorption 210 mμ (log ε 4.10); ir 1768, 1740, 1650, 1250 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.44; H, 7.92.

The third fraction crystallized from isopropyl ether to give prisms (91 mg) of the β isomer **16**: mp 127–128°; $[\alpha]^{25}D$ +42.5° (*c* 0.27, CH_3OH); uv end absorption 210 mμ (log ε 4.02); ir 1769, 1739, 1667, 1653, and 1251 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.29; H, 7.67.

Dihydro-β-cycloepitulipinolide (18) and β-Isocycloepitulipinolide (33).—β-Cycloepitulipinolide (**16**) (120 mg) in 10 ml of absolute C_2H_5OH was hydrogenated over 60 mg of 5% Pd on charcoal as catalyst at atmospheric pressure and ambient temperature. The reduction was terminated after uptake of 1 mol equiv of hydrogen, the catalyst was removed by filtration, and the residue remaining after evaporation of solvent was crystallized from isopropyl ether to give prisms (42 mg) of **18**: mp 160–161°; $[\alpha]^{25}D$ +65.5° (*c* 0.625, CH_3OH); ir 1774 (γ-lactone), 1740 (acetate), 1650 (olefin), and 1240 cm^{-1} (C–O–C).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.95; H, 8.20.

The mother liquor residues (260 mg) from a number of hydrogenations were chromatographed on columns employing 5% $AgNO_3$-treated plates and ether–isopropyl ether (1:9) as solvent. The first few fractions gave an oil (37 mg) lacking olefin bands in the ir and were not further investigated. The second fraction (179 mg) crystallized from isopropyl ether as flattened cubes of β-isocycloepitulipinolide (**33**): mp 111–112°; $[\alpha]^{25}D$ +103° (*c* 0.31, CH_3OH); uv max 218 mμ (log ε 3.99); ir 1750 (γ-lactone), 1685, and 1650 cm^{-1} (olefins).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.01; H, 7.29.

Hydrolysis of Dihydro-β-cycloepitulipinolide (18) to the Hydroxylactone 19.—A solution of 140 mg of **18** in 5 ml of CH_3OH originally treated with 23 mg of Na was kept at ambient temperature for 20 hr. The solution was then diluted with 10 ml of H_2O, acidified with acetic acid, and extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ extract was washed with 5% $NaHCO_3$ and H_2O and dried (Na_2SO_4). On solvent evaporation a residue was left (101 mg) that crystallized from isopropyl ether to give 71 mg of **19** as needles: mp 154–156°; $[\alpha]^{25}D$ +75.3° (*c* 0.465, CH_3OH); ir 3581 and 3410 (hydroxyl), 1768 (γ-lactone), and 1648 cm^{-1} (olefin). In other runs, the same product was obtained in the same yield when the acidification step was omitted.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.43; H, 8.68.

β-Cycloisoepitulipinolide (20).—The hydroxylactone **19** (49 mg) in 0.75 ml of pyridine was treated with the same volume of acetic anhydride. About 20 hr later the solution was diluted with 180 ml of ether and extracted successively with 25-ml portions of 5% oxalic acid, 5% $NaHCO_3$, and water. The dried (Na_2SO_4) ether solution on evaporation left 50 mg of a residue that crystallized from isopropyl ether as feathery needles of **20** (41 mg): mp 150–151°; $[\alpha]^{5}D$ +63.3° (*c* 0.30, CH_3OH); ir 1773 (γ-lactone), 1729 (acetate), 1650 (olefin), and 1250 cm^{-1} (C–O–C).

Ancl. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.56; H, 8.60.

Oxidation of the Hydroxylactone 19 to the Ketone 21.—To the hydroxylactone **19** (49 mg) in 0.2 ml of $(CH_3)_2SO$ was added 0.5 g of dicyclohexylcarbodiimide, 0.2 ml of 1 m*M* H_3PO_4 in $(CH_3)_2SO$, and 2 ml of C_6H_6. After 30 hr at ambient temperature the mixture was diluted with 50 ml of ethyl acetate and 0.5 gm of oxalic acid in 2 ml of CH_3OH was added. The precipitated dicyclohexylurea was collected after 30 min and the filtrate was washed with two 10-ml portions of water, dried (Na_2SO_4), and evaporated. The small amount of the urea still contaminating the residue was removed by mixing with diethyl ether and filtering. The filtrate residue (31 mg) crystallized from isopropyl ether as prisms (15 mg) of **21**: mp 152–154°; $[\alpha]^{25}D$ +110° (*c* 0.10, CH_3OH); uv max 285 mμ (ε 31); ir 1775 (γ-lactone), and 1721 cm^{-1} (cyclohexanone).[29]

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.71; H, 8.39.

Hydrolysis of Dihydro-β-cycloepitulipinolide (18) to the Hydroxy Acid 22.—A solution of 206 mg of **18** in 40 ml of C_2H_5OH was stirred with 300 mg of Na_2CO_3 in 60 ml of H_2O for 20 hr. Acidification with acetic acid was followed by extraction with three 50-ml portions of $CHCl_3$ and drying of the extract with Na_2SO_4. The residue (150 mg) from the $CHCl_3$ extract crystallized to give 110 mg of silky needles of **22**: mp 170–171°; $[\alpha]^{25}D$ −33.3° (*c* 0.18, CH_3OH); ir 3587 (hydroxyl), 1734 (acetate),

1701 cm^{-1} (carboxyl), as well as the characteristic broad absorption between 3400 and 3000 cm^{-1} for carboxylic acids.

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.49; H, 7.68.

Hydrolysis of γ-Cycloeptiulipinolide (17) to the Hydroxy Acid 23.—A solution of **17** (265 mg) in 50 ml of C_2H_5OH and a solution of 300 mg of Na_2CO_3 in 75 ml of H_2O were stirred together for 20 hr. The reaction mixture was acidified with acetic acid and extracted with chloroform, and the solvent was evaporated after drying (Na_2SO_4) to leave a 200 mg residue. Crystallization from isopropyl ether gave fine needles (150 mg) of **23**: mp 147–149°; $[\alpha]^{25}D$ −21.8° (*c* 0.55, CH_3OH); ir 3600 (hydroxyl), 1735 (acetate), and 1694 cm^{-1} (α,β-unsaturated carboxylic acid), as well as the typical broad band between 3400 and 3050 cm^{-} for carboxylic acids.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.43; H, 7.89.

Methylation of Hydroxy Acid 23 to the Ester 24.—The hydroxy acid **23** (50 mg) dissolved in 3 drops of C_2H_5OH was diluted with 10 ml of diethyl ether and cooled to 5°. An ethereal solution of CH_2N_2 was added while stirring until a persistent yellow color was reached. Evaporation of the solvent left a crystalline mass (55 mg) that was recrystallized from isopropyl ether to give 30 mg of the ester **24** as needles: mp 131–131.5°; $[\alpha]^{25}D$ −21.8° (c 0.505, CH_3OH); ir 3600 and 3500 (hydroxyl), 1732 (acetate), and 1727 cm^{-1} (methyl ester).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.89; H, 8.41.

Ozonolysis of Dihydro-β-cycloepitulipinolide (18) to the Ketone 25.—Oxygen containing about 3% ozone was passed through an acetic acid solution of 200 mg of **18** for 25 min while cooling at 10°. The reaction mixture was diluted with 100 ml of ether and shaken with 1.0 g of Zn dust for 30 min. Removal of the Zn and evaporation of the filtrate gave a crystalline residue (125 mg) which was recrystallized from absolute C_2H_5OH to give fine needles (97 mg) of ketone **25**: mp 210° after yellowing at 190°; $[\alpha]^{25}D$ +27.3° (*c* 0.55, CH_3OH); CD (*c* 0.095, CH_3OH), 25°, $[\theta]_{290}$ −3870; uv max 285 mμ (ε 26.5); ir 1776 (γ-lactone), 1739 (acetate), and 1720 cm^{-1} (cyclohexanone).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.49; H, 7.68.

Deacetylepitulipinolide (Eupatolide) (26).—Epitulipinolide (**3**) (100 mg) was stirred in 20 ml of 60% aqueous CH_3OH containing 100 mg of KOH. After 20 hr at ambient temperature the CH_3OH was removed by evaporation and the aqueous solution acidified with 1 *N* H_2SO_4 to give a cloudy suspension. The mixture was extracted with three 50-ml portions of diethyl ether and the combined extract washed with 5% $NaHCO_4$ and H_2O and then dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue from isopropyl ether gave fine prisms of deacetylepitulipinolide (**26**): mp 186–188° (lit.[19] mp 182–188° as eupatolide); $[\alpha]^{25}D$ +29.7° (*c* 1.88, acetone); ir 3400 (hydroxyl), 1757 (γ-lactone), and 1652 cm^{-1} (olefin).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.34; H, 8.46.

It was not possible to apply Brewster's method[21] for determining the configuration of the hydroxyl in **26** as the benzoate ester could not be made by treating **26** with benzoyl chloride in pyridine or by refluxing with benzoic anhydride in pyridine.

In applying the Horeau procedure, 240.7 mg of α-phenybutyric anhydride and 72.0 mg of **26** in 2.5 ml of pyridine were allowed to react for 16 hr, then 1 ml of H_2O was added, and 141.0 mg of α-phenylbutyric acid, $[\alpha]^{25}D$ −8.7° (*c* 2.82, C_6H_6), was isolated as previously described.[23] The optical yield of (−) 39.7% would indicate an *S* configuration; see discussion for analysis of this result. The neutral crystalline fraction (103 mg) from the esterification contained no starting material as shown by the ir spectrum.

Cyclization of Deacetylepitulipinolide (26).—To a solution of 600 mg of **26** in 70 ml of $CHCl_3$ was added 1.0 ml of $SOCl_2$ and after 30 min at ambient temperature the solution was evaporated at reduced pressure. The residue deposited silky needles (150 mg) from isopropyl ether as a first crop (fraction A) and mostly prisms (250 mg) as a second crop (fraction B). Both fractions were mixtures as evidenced by tlc and nmr. Recrystallization of A (mixture of α and γ isomers) from isopropyl ether–C_2H_5OH gave pure deacetyl-γ-cycloepitulipinolide (**29**) (50 mg): mp 202–203°; $[\alpha]^{25}D$ −63.2° (*c* 0.245, CH_3OH); ir 3600 and 3400 (hydroxyl), 1776 (γ-lactone), and 1670 cm^{-1} (olefin).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.19; H, 8.23.

Chromatography of fraction B on 14 gm of 5% $AgNO_3$-impregnated adsorbent and elution with ether resulted in two fractions. The first a mixture of α and γ isomers yielded more (51 mg) of the crystalline γ isomer **29**. The second (93 mg) was essentially pure deacetyl-β-cycloepitulipinolide (**28**) which crystallized from isopropyl ether–C_2H_5OH as prisms: mp 140–141°; $[\alpha]^{25}D$ +67.3° (*c* 0.26, CH_3OH); ir 3600 and 3500 (hydroxyl), 1762 (γ-lactone), 1675, and 1652 cm^{-1} (olefins).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.33; H, 8.02.

Although the α isomer was formed in the reaction as evidenced from the nmr spectra of the less polar mother liquors, a pure sample was not available either through repeated crystallization or by column chromatography. Additional quantities of the pure β and γ isomers were obtained by chromatography of mother liquor residues.

Acetylation of Deacetyl-β-cycloepitulipinolide (28) to 16.—A 25-mg sample of **28** was added to 0.5 ml of pyridine and 0.5 ml of acetic anhydride. After 20 hr the reaction mixture was diluted with 50 ml of diethyl ether and extracted successively with 10-ml portions of 5% oxalic acid solution, 5% $NaHCO_3$ solution, and H_2O. The dried (Na_2SO_4) ether solution on evaporation left a residue that from isopropyl ether gave prisms (20 mg) of β-cycloepitulipinolide (**16**), mp 127–128° (undepressed when admixed with authentic **16**); the compound gave the same ir spectrum as that of authentic **16**.

Dihydrodeacetyl-β-cycloepitulipinolide (30) and Deacetyl-β-isocycloepitulipinolide (32).—Deacetyl-β-cycloepitulipinolide (**28**) (76 mg) was hydrogenated in 17 ml of absolute C_2H_5OH over 50 mg of 5% Pd on charcoal as catalyst at ambient temperature and atmospheric pressure. The uptake of 1 mol equiv of hydrogen was rapid (~9 min) and the reaction was stopped; the catalyst was removed by filtration. The residue (64 mg) remaining after evaporation of the solvent gave two spots (R_f 0.35 and 0.25) on tlc with ether as solvent. The major product (R_f 0.35) crystallized from isopropyl ether–absolute C_2H_5OH to give 33 mg of dihydrodeacetyl-β-cycloepitulipinolide (**30**): mp 169–170°; $[\alpha]^{25}D$ +87.5° (*c* 0.24, CH_3OH), $[M]^{25}D$ +219°; ir 3400 (hydroxyl), 1760 (γ-lactone), and 1652 cm^{-1} (olefin).

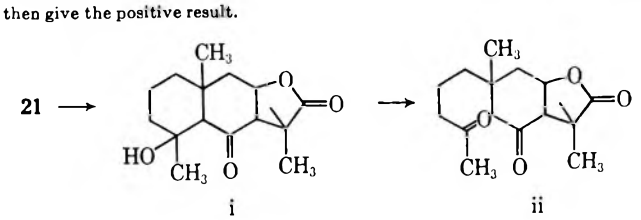
Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86; H, 8.80.

The mother liquor residue (30 mg) was streaked on 1-mm-thick preparative tlc plates and developed by diethyl ether. The R_f 0.25 zone was removed and extracted with $CHCl_3$, and the residue (23 mg) remaining after evaporation of solvent was crystallized as needles from isopropyl ether–C_2H_5OH to give 15 mg of deacetyl-β-isocycloepitulipinolide (**32**): mp 147–148°; $[\alpha]^{25}D$ +100° (*c* 0.15, CH_3OH); ir 3590 and 3440 (hydroxyl), 1750 (γ-lactone), 1685, and 1650 cm^{-1} (olefins).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.59; H, 8.09.

The benzoate ester of **30** was prepared from 39 mg of **30**, 0.5 ml of pyridine, and 0.1 ml of benzoyl chloride. After 24 hr the reaction mixture was treated with 5 ml of H_2O, diluted with 100 ml of ether, and extracted successively with 1 *N* H_2SO_4, H_2O, 5% $NaHCO_3$, and H_2O. The dried (Na_2SO_4) ether phase gave a residue (31 mg) that crystallized from isopropyl ether to give 24 mg of the benzoate as needles: mp 174–174.5°; $[\alpha]^{25}D$ +6.7° (*c* 0.30, CH_3OH), $[M]^{25}D$ +23.7°. The ir lacked -OH absorption but instead had peaks at 1716, 1603, and 1583 cm^{-1}, characteristic of benzoates. The difference in $[M]D$ between the benzoate and the alcohol ($[M]D$ +219°) is −195°, indicating an alcohol with an *R* configuration.[21]

(29) Ketone **21** gave a strongly positive Zimmerman's test[30] and was interpreted as resulting from the production of the diketone ii by the retroaldol opening of the β-hydroxy ketone i formed under the strongly alkaline conditions of the test. The generated α-methylene keto groups in ii would then give the positive result.



(30) R. Neher, "Steroid Chromatography," Elsevier Publishing Co., New York, N. Y., 1964, p 125.

In the Horeau procedure, 83.0 mg of α-phenylbutyric anhydride and 25.0 mg of **30** in 1 ml of pyridine were allowed to react for 16 hr. The α-phenylbutyric acid, 82.0 mg, $[\alpha]^{25}D$ −3.96° (*c* 1.64, C_6H_6), was isolated as already described.[23] The optical yield of (−) 19.4% suggested an *S* configuration. The neutral fraction on examination in the ir showed no starting material.

Acetylation of Dihydrodeacetyl-β-cycloepitulipinolide (30) to 31.—A 43-mg sample of **30** was dissolved in 0.5 ml of pyridine and 1.0 ml of acetic anhydride added. After 20 hr about 5 g of ice was added followed by 5 ml of 5% $NaHCO_3$ solution. After 1 hr the mixture was extracted with three 25-ml portions of diethyl ether and the extract was washed successively with 1 *N* H_2SO_4, H_2O, 5% $NaHCO_3$, and H_2O again. The dried (Na_2SO_4) ether solution left a residue (50 mg) on evaporation that crystallized from petroleum ether–isopropyl ether as fine rods (33 mg): mp 84–85°; $[\alpha]^{25}D$ +62.6° (*c* 0.335, CH_3OH); ir 1775 (γ-lactone), 1740 (acetate), 1655 (olefin), and 1245 cm^{-1} (C–O–C).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.28; H, 7.90.

Hydrolysis of Epitulipinolide (3) to 34.—To a 2.5 ml of $NaOCH_3$ (from 23 mg of Na) solution in CH_3OH was added 100 mg of **3**. After 20 hr, 5 ml of H_2O was added and the solution was acidified with acetic acid then extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ extract was washed with 5% $NaHCO_3$ solution and H_2O and then dried (Na_2SO_4). The residue (87 mg) after removal of solvent was recrystallized from isopropyl ether–C_2H_5OH forming feathery needles (71 mg) of **34**: mp 138–138.5°; $[\alpha]^{25}D$ +65.0 ± 2.5° (*c* 2.4, $CHCl_3$) {lit.[19] mp 138–139.5°; $[\alpha]^{25}D$ +60.3° (*c* 3.1, $CHCl_3$)}; ir 3600 and 3450 (hydroxyl) and 1757 cm^{-1} (γ-lactone).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.64; H, 8.63.

Oxidation of the Hydroxylactone 34 to the Ketone 35.—The lactone **34** (40 mg) was added to 1 ml of Sarett's reagent (120 mg of CrO_3 in 1 ml of pyridine) and after 24 hr at ambient temperature the mixture was diluted with 45 ml of diethyl ether. The resultant mixture was extracted successively with four 10-ml portions of 2% tartaric acid, 5% $NaHCO_3$, and H_2O, and then dried (Na_2SO_4). Removal of solvent gave an oil (32 mg) that crystallized from isopropyl ether as needles (19 mg) of **35**: mp 87–87.5°; $[\alpha]^{25}D$ −409.5° (*c* 0.21, CH_3OH) (lit.[19] mp 87–87.5°); uv max 303 mμ (ε 456) and end absorption 210 (log ε 3.88); ir 1775 (γ-lactone) and 1707 cm^{-1} (ketone). The product **35** gave a positive Zimmerman's test.[30]

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.94; H, 7.95.

Oxidation of the Hydroxylactone 26 to the Ketone 36.—The lactone **26** (124 mg) was dissolved in 20 ml of acetone and after cooling the solution to −5°, Jones reagent[10] (0.20 ml) was added while stirring. The reaction was stopped after 6 min by the addition of 2 ml of CH_3OH. The mixture was filtered and the filtrate diluted with 50 ml of H_2O and extracted with two 250-ml portions of diethyl ether. The ether extract was washed with 5% $NaHCO_3$ and H_2O and then dried (Na_2SO_4). The crystalline residue (85 mg) remaining on evaporation of the solvent was recrystallized from petroleum ether–C_2H_5OH to give 74 mg of needles of **36**: mp 127–128°; $[\alpha]^{25}D$ −563° (*c* 0.37, CH_3OH); uv max 308 mμ (ε 338) and end absolution at 210 (log ε 4.14); ir 1774 (γ-lactone), 1703 (ketone), and 1660 cm^{-1} (olefin). Ketone **36** gave a positive Zimmerman's test.[30]

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.20; H, 7.44.

Registry No.—**1**, 553-21-9; **2**, 24164-12-3; **3**, 24164-13-4; **4**, 24164-14-5; **5**, 24164-15-6; **6**, 24164-16-7; **8**, 2221-81-0; **9**, 2221-82-1; **10**, 24164-19-0; **11**, 24164-20-3; **12**, 24164-21-4; **13**, 24164-22-5; **13** benzoate, 24164-23-6; **14**, 24164-24-7; **15**, 24215-66-5; **16**, 24164-25-8; **17**, 24164-26-9; **18**, 24164-27-0; **19**, 24164-28-1; **20**, 24164-29-2; **21**, 24164-30-5; **22**, 24164-31-6; **23**, 24164-32-7; **24**, 24164-33-8; **25**, 24164-34-9; **26**, 24164-35-0; **28**, 24164-36-1; **29**, 24164-37-2; **30**, 24164-38-3; **30** benzoate, 24165-30-8; **31**, 24165-31-9; **32**, 24165-32-0; **33**, 24165-33-1; **34**, 24165-34-2; **35**, 24165-35-3; **36**, 24165-36-4.

Dimethyl Sulfoxide Oxidation of the Hydroxy Group in Steroids

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The acid-catalyzed reactions between diphenylketene-*p*-tolylimine and DMSO, N,N-diethylaminoprop-1-yne and DMSO, and N,N-dimethylaminophenylacetylene and DMSO have been used to effect the oxidation of the hydroxy group in a number of steroids. These reactions illustrate some interesting variations of the well-known oxidation procedure of Moffatt, *et al.*, involving dicyclohexylcarbodiimide and DMSO. The mechanism of the ynamine–DMSO oxidation has been investigated.

The acid-catalyzed dimethyl sulfoxide (DMSO)–dicyclohexylcarbodiimide (DDC) oxidation of alcohols to the corresponding aldehydes and ketones has been reported by Moffatt, *et al.*[1,2] In this connection, our preliminary investigation demonstrated the application of diphenylketene-*p*-tolylimine–dimethyl sulfoxide[3] and N,N-diethylaminoprop-1-yne–dimethyl sulfoxide[4] for the oxidation of the hydroxy group in steroids. Recently, we have also reported on the mechanism of ketenimine–DMSO and carbodiimide–DMSO oxidations.[5] Our results based on nuclear magnetic resonance spectroscopy using hexadeuteriodimethyl sulfoxide (DMSO-d_6) substantiated the stepwise mechanism for the DCC–DMSO oxidation as proposed by Moffatt, *et al.*,[6] and refuted Torsell's three-body concerted mechanism.[7] In this paper, we wish to illustrate the usefulness of the reagents ynamine–DMSO and ketenimine–DMSO in the oxidation of the hydroxy group in steroids and propose a mechanism for the ynamine–DMSO oxidation.

During the past 2–3 years, interest in the chemistry and application of ynamines has increased considerably. It has been shown that they undergo some very interesting reactions. For instance, they have been reported to undergo reactions analogous to carbodiimides and ketenimines.[8–11] Based on these observations, we re-

(1) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661 (1965).
(2) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5670 (1965).
(3) R. E. Harmon, C. V. Zenarosa, and S. K. Gupta, *Chem. Ind.* (London), 1428 (1969).
(4) R. E. Harmon, C. V. Zenarosa, and S. K. Gupta, *Chem. Commun.*, **537** (1969).
(5) R. E. Harmon, C. V. Zenarosa, and S. K. Gupta, *Tetrahedron Lett.*, 3781 (1969).
(6) J. G. Moffatt and A. H. Fenselau, *J. Amer. Chem. Soc.*, **88**, 1762 (1966).
(7) K. Torsell, *Tetrahedron Lett.*, 4445 (1966).
(8) R. Buijle and H. G. Viehe, *Angew. Chem. Int. Ed. Engl.*, **3**, 582 (1964).
(9) H. S. Mourik, E. Harryvan, and J. F. Arens, *Rec. Trav. Chim. Pays-Bas*, **84**, 1344 (1965).
(10) H. G. Viehe, *Angew. Chem. Int. Ed. Engl.*, **6**, 767 (1967).
(11) F. Waygand, W. Konig, R. Buijle, and H. G. Viehe, *Chem. Ber.*, **98**, 3632 (1965).

Table I

DMSO Oxidation of Hydroxy Steroids Using the Ynamines 1 and 3

Reactant	Product	Mp, °C	Lit. mp, °C	Yield, %, using the ynamine 1	Yield, %, using the ynamine 3
Testosterone	4-Androstene-3,17-dione[a]	169–170	169–170[b]	60	70
5-Cholesten-3β-ol	5-Cholesten-3-one	119–121	119–120[c]	55	
4-Pregnen-11α-ol-3,20-dione	4-Pregnene-3,11,20-trione[a]	172–175	172–175[b]	53	62
5-Androsten-3β-ol-17-one	5-Androstene-3,17-dione[d]	130–146	130–145[b]	60	70
5-Androstene-3β,17β-diol	5-Androstene-3,17-dione[d]	130–145	130–145[b]	45	55

[a] Recrystallized from methanol. [b] D. H. Peterson, H. C. Murry, S. H. Eppstein, L. M. Reinke, A. Weintraub, F. D. Meister, and H. M. Leigh, *J. Amer. Chem. Soc.*, **87**, 5690 (1965). [c] L. Ruzicka and W. Borshard, *Helv. Chim. Acta*, **20**, 244 (1947). [d] Recrystallized from absolute ethanol.

Table II

DMSO Oxidation of Hydroxy Steroids Using the Ketenimine 5

Reactant	Product[a]	Mp, °C	Yield, %
Testosterone	4-Androstene-3,17-dione	169–171	82
4-Pregnene-11α-ol-3,20-dione	4-Pregnene-3,11,20-trione	172–175	62
5-Androstene-3β,17β-diol	5-Androstene-3,17-dione	130–146	60
5-Cholestan-3β-ol	5-Cholesten-3-one	119–120	69

[a] For literature melting point and solvent used for recrystallization, see Table I.

cently reported the first example of the use of alkynylamine for the oxidation of the hydroxy group in steroids.[4] Now, we have investigated this problem in greater detail. We have accomplished the oxidation of a number of hydroxy steroids using N,N-diethylaminoprop-1-yne (**1**) and N,N-dimethylaminophenylacetylene (**3**) (eq 1 and 2). The ynamine **1** was commercially available.

$$\underset{\mathbf{1}}{CH_3C{\equiv}CNEt_2} + (CH_3)_2SO + R_2CHOH \xrightarrow{H_3PO_4} \underset{\mathbf{2}}{CH_3CH_2\overset{O}{\overset{\|}{C}}NEt_2} + CH_3SCH_3 + R_2C{=}O \quad (1)$$

$$\underset{\mathbf{3}}{PhC{\equiv}CNMe_2} + (CH_3)_2SO + R_2CHOH \xrightarrow{H_3PO_4} \underset{\mathbf{4}}{PhCH_2\overset{O}{\overset{\|}{C}}NMe_2} + CH_3SCH_3 + R_2C{=}O \quad (2)$$

For the preparation of the ynamine **3**, 1-chloro-2-phenylacetylene was prepared by the reaction of phenylacetylene with benzenesulfonyl chloride in the presence of sodamide.[12] Treatment of 1-chloro-2-phenylacetylene with trimethylamine yielded N,N-dimethylaminophenylacetylene (**3**).[13] The oxidations of the hydroxy steroids (1 mmol) were conducted in anhydrous DMSO–benzene solutions containing an excess of the ynamines **1** or **3** (5 mmol) and only catalytic amount of 100% orthophosphoric acid (H_3PO_4). It was necessary to cool the reaction mixture to 0° to prevent polymerization of the ynamine. The progress of these reactions was followed by thin layer chromatography in chloroform–ethyl acetate (4:1). In all the cases, the oxidized steroids were isolated by column chromatography on silica gel. The results of hydroxy steroids oxidized using the ynamines **1** and **3** are summarized in Table I. The products were characterized, wherever possible, by undepressed mixture melting points and superimposable infrared spectra with those of authentic samples. Apparently, the ynamine **3** afforded higher yields (of the keto steroids) than the ynamine **1**.

Next, we investigated the oxidation of hydroxy steroids using the reaction of diphenylketene-*p*-tolylimine (**5**) with DMSO (eq 3). These oxidations were conducted

$$\underset{\mathbf{5}}{Ph_2C{=}C{=}N{-}C_6H_4{-}CH_3} + (CH_3)_2SO + R_2CHOH \xrightarrow{H_3PO_4} \underset{\mathbf{6}}{Ph_2\overset{H}{\overset{|}{C}}{-}\overset{O}{\overset{\|}{C}}NH{-}C_6H_4{-}CH_3} + R_2C{=}O + CH_3SCH_3 \quad (3)$$

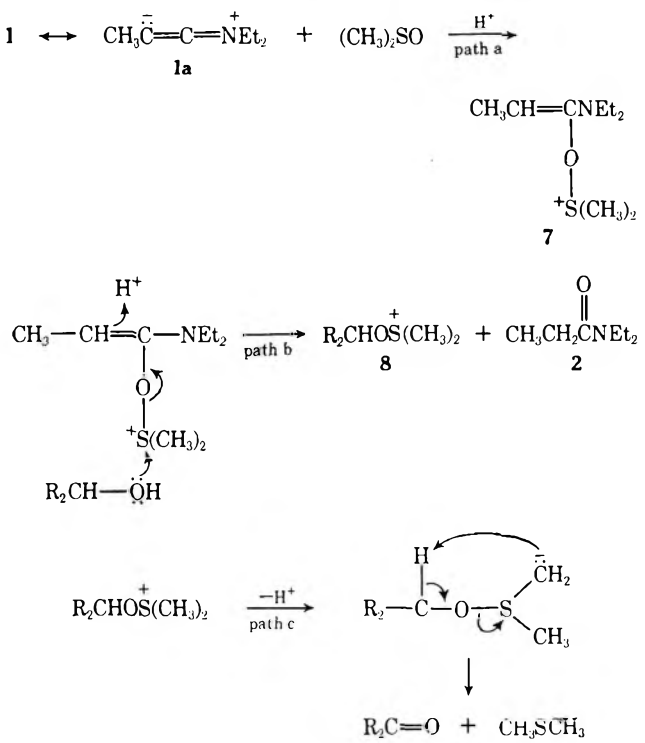
in absolutely anhydrous conditions, as the presence of water causes a competing side reaction resulting in the formation of N-(*p*-tolyl)-α-hydroxydiphenylacetamide. In this procedure, the hydroxy steroid (5 mmol) was added to a solution containing the ketenimine **5** (20 mmol), DMSO, benzene, and catalytic amount of H_3PO_4. The reaction mixtures were stirred at room temperature during 1–2 days. The keto steroids were isolated by column chromatography over silica gel. The results are summarized in Table II. Using this method, the yields of the keto steroids were, generally, higher than those obtained from the ynamine–DMSO oxidations (Table I).

Mechanism of Ynamine–DMSO Oxidation.—Our proposed mechanism for the ynamine–DMSO oxidation is very similar to the mechanism of ketenimine–DMSO[5] and carbodiimide–DMSO oxidations.[6] It is outlined in Scheme I. The first step (step a) involves the formation of N,N-diethylaminoprop-1-yne (**1**)–DMSO adduct **7**. The second step (step b) consists of nucleophilic attack by the alcohol on the sulfoxonium ion **7** resulting in the formation of alkoxylsulfonium ion **8** and N,N-diethylpropionamide **2**. The final step (step c) involves the abstraction of a proton from the α carbon of the alkoxy group in **8** and concerted collapse of the resulting ylide intermediate to the carbonyl compound

(12) R. Truchet, *Ann. Chim.* (Paris), **26**, 309 (1931).

(13) R. Fuks and H. G. Viehe (private communication), *Chem. Ber.*, in press.

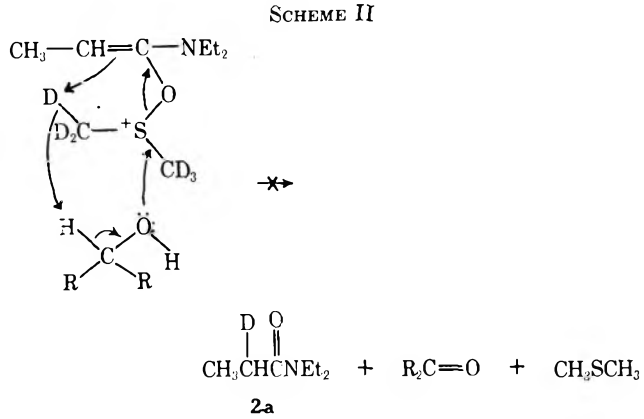
SCHEME I



and dimethyl sulfide. This proposed mechanism was substantiated by the following observations.

In the first step, the ynamine **1**, apparently, reacts as a zwitterion, **1a**, which is structurally similar to a ketenimine. Diphenylketene-*p*-tolylimine and DCC have been reported to form adducts with DMSO which are similar to **7**, and there seems to be no doubt about their formation.[6,14] An alternate mechanism for the ynamine–DMSO oxidation which is in agreement with Torsell's views[7] is outlined in Scheme II. To distinguish between these two mechanisms, we conducted the oxidation of testosterone using the ynamine **1**, 100% H_3PO_4, and DMSO-d_6 (instead of DMSO). The infrared spectrum of the resulting N,N-diethylpropionamide **2** showed no C–D absorption. The labeled dimethyl sulfide was isolated from the reaction mixture. Its nuclear magnetic resonance spectrum showed a multiplet at δ 1.88, characteristic of pentadeuteriodimethyl sulfide (CD_3SCD_2H).[7] Furthermore, it was converted into crystalline mercuric chloride complex whose mass spectrum had a peak at *m/e* 67 (90%) and a low intensity peak at *m/e* 68 (10%). The former is attributed to $[CD_3SCD_2H]^+$ and the latter to $[CD_3SCD_3]^+$. Probably the 10% CD_3SCD_3 contamination of CD_3SCD_2H was caused by the direct conversion of excess ynamine **1** into the amide **2**. The formation of CD_3SCD_2H and the amide **2** in this reaction are consistent with the steps b and c of our proposed mechanism (Scheme I) and rule out the possibility of a concerted three-body mechanism (Scheme II) as proposed by Torsell (according to this mechanism, the reaction should have resulted in the amide **2a** whose infrared spectrum should have shown C–D absorption). Finally, to preclude the remote possibility of CD_3SCD_2H resulting from a proton exchange with H_3PO_4, the ynamine **1** was treated with DMSO-d_6 (without the hydroxy steroid) in the presence of H_3PO_4. The resulting dimethyl sulfide was found to be 100% CD_3SCD_3. Therefore, the formation of CD_3SCD_2H during the oxidation of testosterone using the ynamine **1** and DMSO-d_6 can only be explained by the mechanism proposed in Scheme I.

SCHEME II



Summary and Conclusion

The oxidation of the hydroxy group in steroids has been accomplished with the help of N,N-diethylaminoprop-1-yne–DMSO, N,N-dimethylaminophenylacetylene–DMSO, and diphenylketene-*p*-tolylimine–DMSO. Out of these three reagents, the last one appears to give the best yields of the oxidation products. A stepwise mechanism similar to those proposed for the DCC–DMSO and ketenimine–DMSO oxidations, has been postulated.

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 record the infrared spectra. The nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as internal standard. Mass spectral data was obtained on an Atlas CH-4 mass spectrometer. Silica gel G from Brinkman Instruments was used for thin layer chromatography either on glass slides or 5 × 20 cm glass plates. Spots on the plates were detected either by iodine vapor or by 6 *N* sulfuric acid spray followed by baking at 100° (*ca.* 15 min). Column chromatography was carried out on 2.7 × 30 cm glass columns packed with chromatography grade silica gel. DMSO was distilled from calcium hydride and stored over Linde Molecular Sieves (4a, 1–16 mesh). Hexadeuteriodimethyl sulfoxide (DMSO-d_6) was also dried over molecular sieves. Pyridine was distilled over phosphorous pentoxide and stored over potassium hydroxide. Petroleum ether (bp 30–60°) was distilled over sodium. Diphenylketene-*p*-tolylimine (**5**) was prepared by the procedure of Stevens and Singhal.[15] N,N-Diethyl-1-propyne (**1**), obtained from Fluka AG Chemische Fabrik, Switzerland, was dried over molecular sieves and distilled under reduced pressure.

Preparation of N,N-Dimethylaminophenylacetylene (3).—1-Chloro-2-phenylacetylene was prepared by the reaction of phenylacetylene with benzenesulfonyl chloride in the presence of sodamide.[12] For the preparation of the ynamine **3**, trimethylamine (21.7 g) and 1-chloro-2-phenylacetylene (15 g) were mixed in a stainless steel autoclave and allowed to react at 55° for 40 hr. After that, the autoclave was cooled to room temperature; the reaction mixture was extracted with anhydrous petroleum ether. Evaporation of the solvent and vacuum distillation of the residue yielded 7 g of a light brown oil, bp 90° (40 mm). This oil was redistilled to give the ynamine **3**: 5 g, 31% yield; bp 70° (1 mm); $n^{25}D$ 1.5849; nmr δ 2.65 (s, 6, CH_3), 7.25 (m, 5, Ar-H).

(14) L. Lillien, *J. Org. Chem.*, **29**, 1631 (1964).

(15) C. L. Stevens and G. H. Singhal, *ibid.*, **29**, 34 (1964).

General Procedure for DMSO Oxidation Using Ynamines 1 and 3.—The ynamine 1 (or 3) (15 mmol) was added with stirring to a solution of the hydroxy steroid (3 mmol) in benzene (3 ml) and DMSO (3 ml). The solution was cooled to about 5° and 100% H_3PO_4 was added to it dropwise with stirring. The reaction mixture was allowed to stir at room temperature. The progress of the reaction was followed by tlc in chloroform–ethylacetate (4:1). After the oxidation was over, the reaction mixture was poured into ice–water (*ca.* 300 ml). The resulting precipitate was filtered to give a light yellow solid. This yellow solid was chromatographed over a column of silica gel G. Elution with chloroform–ethyl acetate (4:1) afforded in succession N,N-diethylpropionamide (2) or N,N-dimethylphenylacetamide (4), a small amount of some unidentifiable material, the desired keto steroid, and finally the unreacted starting hydroxy steroid, if any. The keto steroids, thus obtained, were characterized by melting point and ir and uv spectroscopy. Their identity was established by undepressed mixture melting points and superimposable ir spectra with those of authentic samples. The results are summarized in Table I.

General Procedure for Diphenylketene-*p*-tolylimine (5)–DMSO Oxidation.—The hydroxy steroid (5 mmol) was added with stirring to a solution containing diphenylketene-*p*-tolylimine (5) (20 mmol), DMSO (5 ml), benzene (3 ml), and 100% H_3PO_4 (0.6 mmol). The reaction mixture was stirred at room temperature for 1–2 days. The progress of the reaction was followed by tlc in chloroform–ethyl acetate (4:1). After the oxidation was over, the reaction mixture was diluted with benzene (200 ml) and washed first with a solution of sodium hydrogen carbonate (10%) and then water. The solution was dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil which was chromatographed over a column of silica gel. Elution with chloroform–ethyl acetate (4:1) gave in succession N-(*p*-tolyl)diphenylacetamide (6), a small amount of some unidentified material, the oxidized steroid, and finally any unreacted hydroxy steroid. As before, the products were identified by undepressed mixture melting points and superimpossable ir spectra with those of authentic samples. The yields of keto steroids, thus obtained, were higher than those obtained from ynamine–DMSO oxidations. The results are summarized in Table II.

Oxidation of Testosterone Using the Ynamine 1 and DMSO-d_6.—The oxidation was carried out in a 50-ml three-necked round-bottom flask connected to a trap cooled at −70° by using a Dry Ice–acetone bath. The procedure and the amounts of the reactants were exactly the same as described in the general procedure. After the oxidation was over, the dimethyl sulfide formed during the reaction was collected by distillation. For this the reaction mixture was heated at 50° and a smooth stream of nitrogen gas was bubbled through the mixture to facilitate the collection of dimethyl sulfide. The nmr spectrum at 10° of the solution of dimethyl sulfide in benzene, thus obtained, showed a multiplet at δ 1.88, characteristic of pentadeuteriodimethyl sulfide (CD_3SCD_2H). Furthermore, the above benzene solution of dimethyl sulfide was treated with a saturated solution of mercuric chloride in absolute ethanol (4 ml). Filtration yielded 1.3 g of a white powder, mp 152–156°. The solid was crystallized from benzene to yield colorless crystals (1 g) of $3HgCl_2 \cdot 2CD_3SCD_2H$, mp 157–158° (lit.[16] mp 158°). The mass spectrum of this complex showed an intense peak at *m/e* 67 (90%) and a weak peak at *m/e* 68 (10%). The former peak was attributed to $[CD_3SCD_2H]^+$ and the latter to $[CD_3SCD_3]^+$. The reaction mixture after the separation of dimethyl sulfide was subjected to fractional distillation at 44–46° under vacuum (1 mm). This afforded N,N-diethylpropionamide 2, as a colorless liquid: nmr ($CDCl_3$) δ 1.6 (m, 9.0, CH_3), 2.32 (q, 2, $CH_2C{=}O$), 3.38 [q, 4, $N(CH_2-)_2$]. The ir spectrum showed the absence of any C–D absorption. The residue was subjected to column chromatography over silica gel. Elution with chloroform–ethyl acetate (4:1) afforded androst-4-ene-3,17-dione (0.39 g, 46%), mp 169–171°. The mixture melting point with an authentic sample (mp 169–171°) was undepressed.

Reaction of the Ynamine 1 with H_3PO_4 and DMSO-d_6.—The ynamine 1 (1.66 g, 15 mmol) was dissolved in a mixture of benzene (1.5 ml) and DMSO-d_6 (1.5 ml). The solution was cooled to about 5° and treated with 100% H_3PO_4 (0.1 g). The reaction was followed by ir spectroscopy using the disappearance of the peak at 2200 cm^{-1} (C≡C). When all the ynamine 1 had been reacted (2 hr), the flask was connected to a trap cooled at −70° (Dry Ice–acetone bath). The reaction mixture was heated at 50° and the solution of dimethyl sulfide in benzene was collected as before. The nmr spectrum of this solution showed no absorption, indicating the absence of any CD_3SCD_2H. Next, the solution was treated with a saturated solution of $HgCl_2$ in absolute ethanol (2 ml). The resulting $3HgCl_2 \cdot 2CD_3SCD_3$ complex (0.39 g) had mp 157–158° (lit.[16] mp 158°). Its mass spectrum showed the absence of a peak at *m/e* 67 due to $[CD_3SCD_2H]^+$. Finally, the reaction mixture remaining after the collection of dimethyl sulfide was subjected to vacuum distillation at 44–46° (1 mm). The nmr spectrum of the resulting N,N-diethylpropionamide (2, 1.69 g) was consistent with the structure.

Registry No.—1, 4231-35-0; 3, 4604-65-3; 5, 5110-54-2; testosterone, 58-22-0; 5-cholesten-3β-ol, 57-88-5; 4-pregnen-11α-ol-3,20-dione, 80-75-1; 5-androsten-3β-ol-17-one, 53-43-0; 5-androstene-3β,17β-diol, 521-17-5.

Acknowledgement.—This work was supported by Grant CA-06140 from the National Cancer Institute.

(16) F. Challenger and M. I. Simpson, *J. Chem. Soc.*, 1591 (1946).

Use of Chloroacetic Anhydride for the Protection of Nucleoside Hydroxyl Groups

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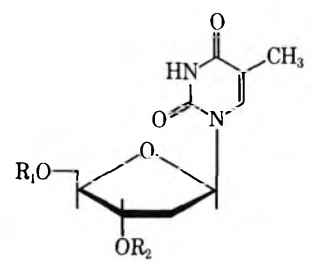
The use of the chloroacetyl group as a protecting group in the nucleoside and nucleotide field has been examined. The reactions of chloroacetic anhydride with the hydroxyl groups of partially protected nucleosides gave good yields of the corresponding chloroacetyl derivatives. Removal of the chloroacetyl group(s) from these compounds was accomplished without loss of other protecting groups. The reagents employed for the removal of chloroacetyl groups included thiourea, 2-mercaptoethylamine, ethylenediamine, and *o*-phenylenediamine. Of these, the most efficient was found to be 2-mercaptoethylamine. The stability of the chloroacetyl group in water, buffered aqueous pyridine, and buffered aqueous 2,6-lutidine has been examined. Chloroacetylation of mononucleotides was readily accomplished, but instability problems prevented the purification of these compounds. Diphenylchloroacetyl chloride reacted selectively with the primary hydroxyl group of thymidine, and a high yield of the 5′ derivative was obtained. Attempts to remove this group with 2-mercaptoethylamine were unsuccessful, although cleavage was effected using thiourea or aqueous ammonia.

Chemical manipulations in the nucleoside and nucleotide fields are often governed by the feasibility of differential protection and removal of the protecting groups employed in a particular synthesis. The value of acid-labile protecting groups is sometimes limited by the lability of the purine–glycosyl bond of nucleosides and nucleotides, particularly when the purine bears an N-acyl group. The extremely acid-sensitive di-O-*p*-methoxytrityl group, for example, cannot be removed from N-benzoyldeoxyadenosine derivatives without a substantial amount of concomitant depurination.[1,2] Acyl groups, on the other hand, are widely used as base-labile groups for the protection of amino and hydroxyl functions. Thus, other protecting groups, which do not require acidic or basic conditions for their removal, and hence are compatible with the N-benzoyldeoxyadenosine moiety, may be useful in the chemical manipulation of these materials. Hydroxyl protecting groups which can be removed under conditions close to neutrality have already been employed in the nucleoside field. The dinitrobenzenesulfenyl moiety has been successfully removed from N-benzoyldeoxyadenosine derivatives using thiophenol or hydrogen sulfide,[3] and β-benzoylpropionyl esters have been cleaved with buffered hydrazine.[4] A dihydrothiophene adduct with 5′-O-acetylthymidine has been removed with silver ion,[5] and β,β,β-tribromoethoxycarbonyl derivatives have been deshielded using a zinc–copper couple.[6] Recent reports on the protection of amino and hydroxyl functions with the chloroacetyl group[7,8] and subsequent deprotection under mild conditions prompted our investigation into the utility of the chloroacetyl group for the protection of nucleoside hydroxyl functions.

While the reactions between nucleosides and chloroacetyl chloride were generally unsatisfactory, giving intractable mixtures, the reactions with chloroacetic anhydride proceeded smoothly at 0° with no major byproducts. The reaction of chloroacetic anhydride with 3′-O-acetylthymidine (**1**) required 2 hr for completion, and the corresponding 5′-chloroacetate **2** was isolated in crystalline form. The presence of the chloroacetate group in the product, as well as in all other chloroacetyl derivatives isolated, was readily detected by nmr spectroscopy; each chloroacetyl group gave rise to a sharp singlet in the region δ 4.0–4.5. For removal of the chloroacetyl group from the **2**, the compound was treated with thiourea in refluxing ethanol.



1, $R_1 = H$; $R_2 = COCH_3$
2, $R_1 = COCH_2Cl$; $R_2 = COCH_3$
3, $R_1 = C(C_6H_5)_3$; $R_2 = H$
4, $R_1 = C(C_6H_5)_3$; $R_2 = COCH_2Cl$
5, $R_1 = H$; $R_2 = COCH_2Cl$
11, $R_1 = COCl(C_6H_5)_2$; $R_2 = H$
12, $R_1 = H$; $R_2 = C(C_6H_5)_2C_6H_4OCH_3$

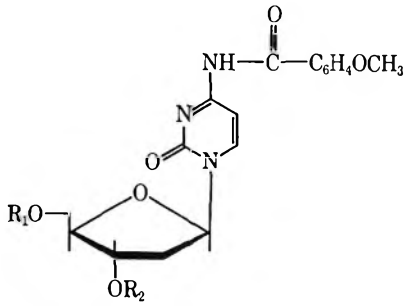
All of the starting material was consumed after 1 hr, and 3′-O-acetylthymidine was isolated from the mixture in 81% yield. As previously described,[7] the removal of chloroacetyl groups probably involves an isothiourea intermediate which undergoes intramolecular amidinolysis with formation of the alcohol and a pseudothiohydantoin.[9]

5′-O-Tritylthymidine (**3**) also afforded a chloroacetyl derivative **4** which was isolated without difficulty. Removal of the chloroacetyl group from **4** using thiourea in ethanol was unsatisfactory since this reaction was accompanied by extensive detritylation. This problem was avoided by the use of pyridine as cosolvent, and 5′-O-tritylthymidine (**3**) was recovered in good yield. Thus, the conditions required for the introduction and removal of the chloroacetyl group are completely compatible with the commonly used trityl and acetyl protecting groups. The trityl group was removed from **4** using 80% acetic acid at 100° for 30 min, and these conditions did not affect the chloroacetyl group; 3′-O-chloroacetylthymidine (**5**) was isolated in good yield.

In the deoxycytidine series, N-anisoyl-5′-O-mono-*p*-methoxytrityldeoxycytidine (**6**)[1] gave a 3′-chloroacetyl

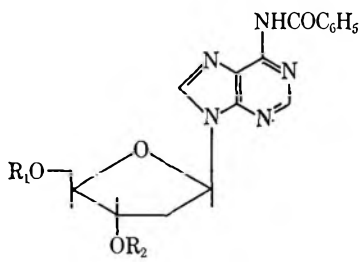
(1) H. Schaller, G. Weimann, B. Lerch, and H. G. Khorana, *J. Amer. Chem. Soc.*, **85**, 3821 (1963).
(2) M. W. Moon, S. Nishimura, and H. G. Khorana, *Biochemistry*, **5**, 937 (1966).
(3) G. W. Grams and R. L. Letsinger, *J. Org. Chem.*, **33**, 2589 (1968).
(4) R. L. Letsinger, M. H. Caruthers, P. S. Miller, and K. K. Ogilvie, *J. Amer. Chem. Soc.*, **89**, 7146 (1967).
(5) L. A. Cohen and J. A. Steele, *J. Org. Chem.*, **31**, 2333 (1966).
(6) A. F. Cook, *ibid.*, **33**, 3589 (1968).
(7) M. Masaki, T. Kitahara, H. Kurita, and M. Ohta, *J. Amer. Chem. Soc.*, **90**, 4508 (1968).
(8) A. Fontana and E. Scoffone, *Gazz. Chim. Ital.*, **98**, 1261 (1968).
(9) Pseudothiohydantoins have been prepared by a similar cyclization procedure: C. Liebermann, *Ann. Chem.*, **207**, 121 (1881).

derivative **7** by reaction with chloroacetic anhydride in pyridine at 0° for 4 hr. Treatment with thiourea in ethanol–pyridine in the usual way removed the chloroacetyl group without loss of the other protecting groups, and **6** was recovered by silica gel column chromatography. Removal of the mono-*p*-methoxytrityl group from **7** gave the 5′-hydroxy compound **8**, a partially protected deoxycytidine derivative which may be of use for subsequent transformations.



6, $R_1 = CH_3OC_6H_4(C_6H_5)_2C$; $R_2 = H$
7, $R_1 = CH_3OC_6H_4(C_6H_5)_2C$; $R_2 = COCH_2Cl$
8, $R_1 = H$; $R_2 = COCH_2Cl$

Experiments were also carried out in the deoxyadenosine series in order to determine whether the chloroacetyl group is compatible with the much more labile N-benzoyldeoxyadenosine moiety. No problems were encountered during the chloroacetylation of N-benzoyldeoxyadenosine (**9**),[1] and its 3′,5′-di-O-chloroacetyl derivative **10** was obtained crystalline in good yield. Attempts to remove the chloroacetyl groups with thiourea in ethanol–pyridine were unsuccessful; depurination rapidly occurred, and N-benzoyladenine was isolated in high yield and identified by comparison with a commercially available sample.[10] Depurination also occurred when the reaction was carried out in the presence of triethylamine although none could be detected in a series of control experiments with N-benzoyldeoxyadenosine.



9, $R_1 = H$; $R_2 = H$
10, $R_1 = COCH_2Cl$; $R_2 = COCH_2Cl$

In order to overcome this problem, other reagents for removing the chloroacetyl group were sought. Of the reagents examined, the most satisfactory was found to be 2-mercaptoethylamine hydrochloride; using this reagent in the presence of triethylamine, dechloroacetylation of **10** was complete within 2 hr at room temperature, and no evidence of depurination was detected. Ethylenediamine was also found to be satisfactory, and only traces of debenzoylation were observed. *o*-Phenylenediamine was also quite suitable for dechloroacetylation of **10**, and a high yield of N-benzoyldeoxyadenosine was isolated. This last reagent has been used for the liberation of amino groups from their chloroacetyl amides during peptide synthesis[11] although these reactions were carried out under strongly alkaline conditions. 1,2-Ethanedithiol was also investigated, but it was not found to be suitable; a number of products were observed. In subsequent dechloroacetylation studies, using **2** as a model compound, 2-mercaptoethylamine was again the preferred reagent.

An indication that dechloroacetylation occurs *via* a cyclic intermediate was obtained by the isolation of 1,4-thiazin-3-one from the reaction of **2** with 2-mercaptoethylamine hydrochloride. Thus the thiol group must initially have acted as the nucleophilic agent in the displacement of the chloride ion with the intermediate undergoing intramolecular aminolysis and liberation of the alcohol. The presence of triethylamine is apparently necessary in order to generate the nucleophilic amino group from its hydrochloride salt, since in the absence of base, no dechloroacetylation could be observed. Excess triethylamine was removed at the end of the reaction by evaporation, thus avoiding the alkaline conditions which would produce indiscriminate deacylation. As expected, the free base ethylenediamine was shown to cause debenzoylation of **10** as well as dechloroacetylation, whereas the former reaction was completely eliminated with the use of a limited amount of its hydrochloride in triethylamine. *o*-Phenylenediamine, on the other hand, must be a sufficiently weak base ($pK_B = 9.6$) not to produce deacylation under these conditions.

Chloroacetylation of mononucleotides was also studied. Thymidine 5′-phosphate reacted smoothly with chloroacetic anhydride in pyridine, and paper chromatography of the reaction mixture after 2 hr indicated complete absence of starting material. Upon addition of water, dechloroacetylation began to occur, and attempts to isolate pure chloroacetate were not successful.[12] Similar problems were encountered during attempts to isolate the chloroacetyl derivatives of N-anisoyldeoxycytidine 5′-phosphate and N-benzoyldeoxyadenosine 5′-phosphate. Efforts were therefore made to define the reasons for the instability of the chloroacetyl group. In these experiments, 3′-O-chloroacetylthymidine (**5**) was used as a model compound, and the reactions were monitored by thin layer chromatography followed by elution and spectrophotometric assay of the appropriate spots. The chloroacetate group was relatively stable in water and in 0.2 *M* sodium chloroacetate, pH 6.3; in the latter experiment, a half-time of approximately 100 hr was found for the dechloroacetylation reaction. In aqueous pyridine containing pyridinium chloride or chloroacetate, pH 6–7, the reaction was much more rapid, being complete after 20 hr at room temperature with a half-time of 4 hr. When pyridine was replaced by 2,6-lutidine, deacylation was much slower at the same pH value (half-time 24 hr). These experiments clearly implicate pyridine as the deacylating agent, presumably by nucleophilic attack on the carbon

(10) Obtained from Nutritional Biochemicals Corp., Cleveland, Ohio.

(11) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 3069 (1952).

(12) In contrast, the simpler procedures employed for the isolation of nucleoside chloroacetyl derivatives did not produce significant amounts of dechloroacetylation.

bearing the chlorine atom with the formation of an acylpyridinium intermediate. This latter would be labilized toward hydrolysis as compared with the chloroacetate. 2,6-Lutidine, on the other hand, cannot readily form an acylpyridinium intermediate owing to the steric hindrance of the adjacent methyl groups.

In the reaction of chloroacetic anhydride with thymidine, no substantial degree of specificity was observed. The use of the bulkier diphenylchloroacetyl group was therefore investigated for the protection of primary hydroxyl functions. The reaction of thymidine with diphenylchloroacetyl chloride gave a high yield of the crystalline 5′ derivative **11**, together with a small amount of the 3′,5′-bisdiphenylchloroacetyl compound; no trace of the 3′ isomer was detected. The nmr spectrum of **11** in deuterated dimethyl sulfoxide gave a doublet (J = 4 Hz) for the hydroxyl proton, indicating the presence of a secondary hydroxyl group. Further evidence for the assignment of **11** as the 5′ derivative was obtained by its treatment with mono-*p*-methoxytrityl chloride in pyridine, followed by treatment with ammonia. After column purification a good yield of 3′-O-mono-*p*-methoxytritylthymidine (**12**)[13] was obtained.

The removal of the diphenylchloroacetyl group from **11** could not be accomplished using 2-mercaptoethylamine hydrochloride in the same way as for the chloroacetyl derivative; even at elevated temperatures, only small amounts of thymidine were detected. Thiourea, on the other hand, did produce deacylation, although at a slower rate than that found for chloroacetyl derivatives. A related reaction between ethyl diphenylchloroacetate and thiourea has recently been described.[14] Treatment with aqueous ammonia also cleaved the diphenylchloroacetyl group, and thymidine was readily isolated. This group may therefore be of use as a protecting group for primary hydroxyl functions.

Experimental Section[15]

3′-O-Acetyl-5′-O-chloroacetylthymidine (**2**).—A solution of 3′-O-acetylthymidine (**1**, 1.27 g, 4.5 mmol) and chloroacetic anhydride (2.31 g, 13.5 mmol) in dry pyridine was stored at 0° for 2 hr. Water (5 ml) was added, after 10 min at 0° the solution was evaporated to dryness, and the residue was partitioned between chloroform and water. The chloroform layer was washed twice with water, dried (Na_2SO_4), and evaporated to dryness. Crystallization of the residue from ethanol–hexane gave 1.14 g (71%) of **2**: mp 130–132°; uv max (C_2H_5OH) 265 mμ (ε 9320); ir (KBr) 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.23 (s, 2, $COCH_2Cl$).

Anal. Calcd for $C_{14}H_{17}ClN_2O_7$: C, 46.61; H, 4.75; Cl, 9.89; N, 7.76. Found: C, 46.50; H, 4.78; Cl, 9.85; N, 7.73.

3′-O-Chloroacetyl-5′-O-tritylthymidine (**4**).—A solution of 5′-O-tritylthymidine (**3**, 1.35 g, 2.4 mmol, benzene adduct) in dry pyridine (25 ml) was treated with chloroacetic anhydride (2.07 g, 12.1 mmol) for 3.5 hr at 0°, and the product was poured dropwise with stirring into ice water (2 l.). After storage overnight at 5°, the precipitate was collected, washed with water, and dissolved in chloroform. The chloroform solution was dried (Na_2SO_4), evaporated, and crystallized from ethanol to give 1.27 g (94%) of **4**: mp 185–185.5°; uv max (C_2H_5OH) 264 mμ (ε 9200); ir (KBr) 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.07 (s, 2, $COCH_2Cl$).

Anal. Calcd for $C_{31}H_{29}ClN_2O_6$: C, 66.35; H, 5.23; Cl, 6.32; N, 4.99. Found: C, 66.46; H, 5.35; Cl, 6.20; N, 4.93.

3′-O-Chloroacetylthymidine (**5**).—A solution of **4** (1.0 g, 1.85 mmol) in 80% acetic acid (25 ml) was heated at 100° for 30 min. Crystals of triphenylmethyl alcohol were deposited on cooling and were removed by filtration. The filtrate was evaporated to dryness and extracted with ether (three 30-ml portions), and the residue was crystallized from ethanol–hexane to give 413 mg (73%) of **5**: mp 149.5–150°; uv max (2-propanol) 264 mμ (ε 9980); ir (KBr) 1745 cm^{-1} (C=O); nmr (DMSO-d_6) δ 4.40 (s, 2, $COCH_2Cl$).

Anal. Calcd for $C_{12}H_{15}ClN_2O_6$: C, 45.22; H, 4.71; Cl, 11.12; N, 8.75. Found: C, 45.12; H, 4.47; Cl, 11.12; N, 8.82.

Preparation of 7.—A solution of N-anisoyl-5′-O-mono-*p*-methoxytrityldeoxycytidine (**6**, 1.12 g, 1.8 mmol) in dry pyridine (40 ml) was treated with chloroacetic anhydride (0.98 g, 5.75 mmol) for 4 hr at 0°. Ice–water (20 ml) was added and after 15 min the solution was evaporated to dryness. The residue was partitioned between chloroform and water, and the chloroform layer was washed with water (three portions), dried (Na_2SO_4), and evaporated to a syrup. This material was purified by silica gel column (200 g) chromatography, using chloroform–ethyl acetate (1:2) as the solvent. Fractions 60–140 were evaporated to give **7**, 0.97 g (77%) as a foam: uv max (C_2H_5OH) 286 mμ (ε 21,750); ir (KBr) 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.08 (s, 2, $COCH_2Cl$).

Anal. Calcd for $C_{39}H_{36}ClN_3O_8$: C, 65.96; H, 5.11; Cl, 4.99; N, 5.94. Found: C, 65.64; H, 5.07; Cl, 4.89; N, 5.83.

Removal of the Mono-*p*-methoxytrityl Group from 7.—A solution of **7** (0.86 g, 1.2 mmol) in 80% acetic acid (25 ml) was allowed to stand at room temperature for 1 hr. Since thin layer chromatography of the reaction mixture indicated that substantial amounts of the starting material still remained, the solution was heated at 100° for 15 min. The product was cooled and evaporated to dryness, and the residue was washed with ether (three 20-ml portions). The residue was crystallized from ethanol–hexane to give 360 mg (68%) of **8**: mp 174–178°; uv max (C_2H_5OH) 289 mμ (ε 25,300); ir (KBr) 1760 cm^{-1} (C=O); nmr (DMSO-d_6) δ 4.40 (s, 2, $COCH_2Cl$).

Anal. Calcd for $C_{19}H_{20}ClN_3O_7$: C, 52.12; H, 4.60; Cl, 8.10; N, 9.60. Found: C, 52.29; H, 4.54; Cl, 7.88; N, 9.52.

N-Benzoyl-3′,5′-di-O-chloroacetyldeoxyadenosine (**10**).—A solution of N-benzoyldeoxyadenosine (**9**, 1.10 g, 3.1 mmol) in dry pyridine (15 ml) was treated with chloroacetic anhydride (1.57 g, 9.2 mmol) for 1.5 hr at 0°. Water (15 ml) was added, and after 10 min the mixture was evaporated to dryness. The residue was dissolved in hot ethyl acetate and filtered, and on cooling crystals of **10** 1.04 g (66%) were deposited from the filtrate. Concentration of the mother liquor gave a second crop, 0.19 g (12%): mp 146–147°; uv max (2-propanol) 280 mμ (ε 20,900); ir (KBr) 1770 cm^{-1} (C=O); nmr (DMSO-d_6) δ 4.42, 4.47 (s, 2, $COCH_2Cl$).

Anal. Calcd for $C_{21}H_{19}Cl_2N_5O_6$: C, 49.62; H, 3.77; Cl, 13.93; N, 13.78. Found: C, 49.73; H, 3.60; Cl, 13.96; N, 13.85.

Use of Thiourea for Removal of Chloroacetyl Groups. A. Dechloroacetylation of 2.—A solution of **2** (340 mg, 0.94 mmol) and thiourea (85 mg, 1.1 mmol) in ethanol (20 ml) was heated under reflux for 1 hr, and then evaporated to half-volume. Addition of hexane yielded crystalline 3′-O-acetylthymidine, 218 mg (81%), mp 177° (lit.[16] mp 176°).

B. Dechloroacetylation of 4.—A solution of **4** (952 mg, 1.7 mmol) and thiourea (146 mg, 1.85 mmol) in pyridine (10 ml) and ethanol (2 ml) was heated at 100° for 20 min and then evaporated to dryness. The residue was chromatographed on a silica gel column (150 g) using chloroform–ethyl acetate (1:1) as the solvent. Fractions 57–120 were evaporated and recrystallized from ethanol–hexane to give 572 mg (70%) of 5′-O-tritylthymidine (**3**), mp 125–128° (lit.[16] mp 128°).

C. Removal of the Chloroacetyl Group from 7.—A solution of **7** (505 mg, 0.71 mmol) and thiourea (59 mg, 0.78 mmol) in pyridine (10 ml) and ethanol (1 ml) was heated at 100° for 45 min and then evaporated to dryness. The residue was purified by silica gel column (150 g) chromatography using ethyl acetate–

(13) K. K. Ogilvie and R. L. Letsinger, *J. Org. Chem.*, **32**, 2365 (1967).

(14) A. U. Rahman and H. S. E. Gatica, *Rec. Trav. Chim. Pays-Bas*, **88**, 905 (1969).

(15) Pyridine was dried by storage over Linde Molecular Sieve Type 4A. Merck silica gel (0.05–0.2 mm) was used for silica column chromatography, and fractions of 20 ml were collected. Nuclear magnetic resonance spectra were obtained using a Varian A-60 spectrometer, ultraviolet spectra using a Cary Model 14 instrument, and infrared spectra with a Beckman IR-5 or IR-9. A Thomas–Hoover apparatus was used for melting point determinations.

(16) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 951 (1953).

methanol (40:1) as the eluting solvent. Fractions 35–60 were combined and evaporated to give 318 mg (71%) of **6** as a foam. The ir spectrum (KBr) was identical with that of an authentic sample.[1]

D. Reaction of 10 with Thiourea.—A solution of **10** (496 mg, 0.98 mmol) in pyridine (6 ml) and ethanol (2 ml) was treated with thiourea (78 mg, 0.99 mmol) at 100° for 20 min. The product was evaporated to dryness and the residue was dissolved in hot water. Upon cooling, crystals of N-benzoyladenine, 143 mg (61%), were deposited, mp 237–242° (lit.[17] mp 237–238°).

Dechloroacetylation Using 2-Mercaptoethylamine. A. Dechloroacetylation of 2.—A solution of **2** (1.11 g, 3.1 mmol) and 2-mercaptoethylamine hydrochloride (378 mg, 3.3 mmol) in pyridine (15 ml) and triethylamine (4 ml) was stored at room temperature for 1 hr. The product was evaporated to dryness and purified by silica gel column (200 g) chromatography, using ethyl acetate–acetone (40:1) as the solvent. Fractions 30–150 were evaporated and recrystallized from ethanol–hexane to give 723 mg (83%) of 3′-O-acetylthymidine.

B. Compound 10.—A solution of **10** (0.98 g, 1.9 mmol) and 2-mercaptoethylamine hydrochloride (0.45 g, 4.0 mmol) in pyridine (10 ml), methanol (10 ml), and triethylamine (5 ml) was stored at room temperature for 2 hr and then evaporated to dryness. The residue was applied to a silica gel column (200 g) which was eluted with ethyl acetate–methanol (10:1). Fractions 100–200 were evaporated to give N-benzoyldeoxyadenosine, 647 mg (91%), mp 113–117° (lit.[1] mp 113–115°).

Use of Ethylenediamine for Dechloroacetylation.—A solution of the chloroacetyl compound (2 mmol) in pyridine (30 ml), methanol (20 ml), and triethylamine (5 ml) was treated with ethylenediamine dihydrochloride (2–4 mmol) for 4 hr at room temperature. The product was isolated either by direct crystallization or by partition between chloroform and water and subsequent isolation from the chloroform layer.

***o*-Phenylenediamine as a Dechloroacetylating Agent.**—A solution of the chloroacetyl compound (2 mmol) and *o*-phenylenediamine (2–3 mmol) in pyridine (30 ml) and ethanol (15 ml) was stored overnight at room temperature. The products were isolated as described in the experiments using 2-mercaptoethylamine.

Studies on the Stability of the Chloroacetate Group. A. In Aqueous Pyridine.—A solution of the chloroacetyl derivative **5** (5 mg) in 50% aqueous pyridine, which had been adjusted to pH 6.7 with either hydrochloric or chloroacetic acid, was stored at room temperature. Aliquots (20 μl) were removed at intervals, evaporated to dryness, dissolved in methanol, and chromatographed on a silica thin-layer plate, using ethyl acetate–methanol (10:1) as the developing solvent. The appropriate uv-absorbing spots were removed, extracted with methanol (three 5-ml portions), and measured spectrophotometrically. Dechloroacetylation was complete after 20 hr, with a half-time for the reaction of 4 hr.

B. In Aqueous 2,6-Lutidine.—This experiment was carried out as described in part A. Dechloroacetylation was much slower in this medium with a half-time of 24 hr.

C. In Aqueous Sodium Chloroacetate.—A solution of **5** (5 mg) in aqueous sodium chloroacetate, pH 6.3 (0.2 *M*), was examined at intervals as previously described. After 24 hr, 10% dechloroacetylation was detected.

5′-O-Diphenylchloroacetylthymidine (11).—A 0° solution of thymidine (1.94 g) in dry pyridine (25 ml) was treated with diphenylchloroacetyl chloride (2.33 g) for 4 hr. Methanol (2 ml) was added, and after 2 hr the solution was evaporated to dryness. The residue was dissolved in chloroform (100 ml), extracted with water (three 100-ml portions), dried (Na_2SO_4), and evaporated to dryness. The product was purified by silica gel column (400 g) chromatography using chloroform–ethyl acetate (1:1) as the eluting solvent. Fractions 180–400 were evaporated and recrystallized from ethyl acetate to give 3.3 g (87%) of **11**: mp 177°, uv max (CH_3OH) 265 mμ (ε 9200); ir (KBr) 1740 cm^{-1} (C=O); nmr (DMSO-d_6) δ 5.40 (d, 1, J = 4 Hz, CHOH).

Anal. Calcd for $C_{24}H_{23}ClN_2O_6$: C, 61.22; H, 4.92; Cl, 7.53; N, 5.95. Found: C, 61.42; H, 5.06; Cl, 7.28; N, 5.67.

3′-O-Mono-*p*-methoxytritylthymidine (12).—A solution of **11** (6.55 g) and mono-*p*-methoxytrityl chloride (8.7 g) in pyridine (25 ml) was heated overnight at 100°. Water (10 ml) was added, and after 1 hr the solution was evaporated to dryness and dissolved in methanol (200 ml) and concentrated aqueous ammonia (200 ml). After 66 hr the solution was evaporated to dryness and purified by silica gel column (500 g) chromatography using chloroform–ethyl acetate (2:1) as the solvent. Fractions 140–230 were evaporated to dryness, and the residue was dissolved in chloroform. Addition of hexane precipitated 3′-O-mono-*p*-methoxytritylthymidine, 4.86 g (68%), as white powder, mp 115° (lit.[13] mp 126–128°).

Reaction of 11 with Thiourea.—A solution of **11** (1.46 g, 3.1 mmol) and thiourea (1.40 g, 18.4 mmol) in ethanol (50 ml) was heated under reflux for 48 hr. The product was evaporated to dryness and purified by silica column (250 g) chromatography, using ethyl acetate–methanol (40:1) as the eluting solvent. Fractions 70–240 were evaporated to dryness and recrystallized from ethanol–hexane to give 385 mg (51%) of thymidine, mp 184–186° (lit.[18] mp 185°).

Treatment of 11 with Aqueous Ammonia.—A solution of **11** (1.0 g, 2.1 mmol) in methanol (5 ml) and concentrated aqueous ammonia (5 ml) was stored at room temperature for 48 hr and then evaporated to dryness. The residue was partitioned between chloroform and water, and the aqueous layer was evaporated to dryness and recrystallized from water to give 294 mg (58%) of thymidine, mp 186° (lit.[18] mp 185°).

Registry No.—Chloroacetic anhydride, 541-88-8; **2**, 24299-19-2; **4**, 24299-20-5; **5**, 24343-75-7; **7**, 24299-21-6; **8**, 24343-76-8; **10**, 24299-22-7; **11**, 24299-23-8; **12**, 13084-61-2.

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(17) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **121**, 131 (1937).

(18) P. A. Levene and E. S. London, *ibid.*, **83**, 793 (1929).

Total Synthesis and Stereochemistry of *dl*-Elaeocarpidine[1]

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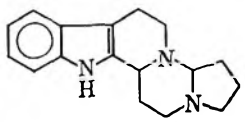
A total synthesis of the novel pentacyclic indole alkaloid elaeocarpidine (**1**) is described. The key amine lactam intermediate **6** undergoes reductive cyclization with lithium aluminum hydride to **1** and dihydroelaeocarpidine (**2**). In the presence of a secondary amine the lithium aluminum hydride reduction is directed almost entirely to cyclization to **1**. The reductive cyclization gives only the naturally occurring epimer, which is suggested to be *cis* on the basis of spectral and chemical data.

Elaeocarpidine (**1**), an indole alkaloid of biogenetic interest, was recently isolated from *Elaeocarpus arch-boldianus* and postulated to have the pentacyclic structure shown.[2] This represents one of only a few indole alkaloids to contain three nitrogen atoms.[3] We now wish to report a simple three-step stereospecific total synthesis of *dl*-elaeocarpidine (**1**) and its hydrogenation product dihydroelaeocarpidine (**2**). The synthesis confirms the proposed structure for **1** and makes available large quantities of **1** and **2** for biological testing and further chemical studies.



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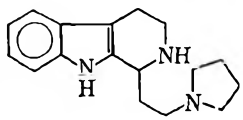


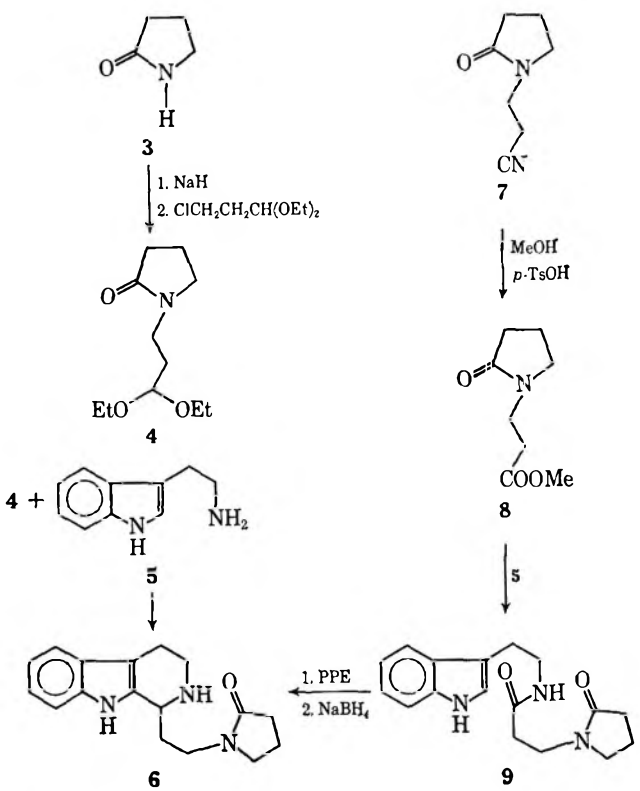
2

After our synthesis was completed, a brief report appeared describing a related preparation of elaeocarpidine and dihydroelaeocarpidine by Harley-Mason and Taylor.[4] Unfortunately, reaction yields and stereochemistry were not discussed in their preliminary publication[4] so a comparison with our synthesis is not presently possible.

Synthesis.—Our synthesis was formulated around two points: the ability of tryptamine (**5**) to condense with aldehydes to form tetrahydro-β-carbolines[5] and the property of lithium aluminum hydride to reduce tertiary amides to the carbinol amine–immonium salt stage.[6,7] Accordingly, our aim was directed toward the synthesis of 1-[2-(2-oxo-N-pyrrolidyl)ethyl]-1,2,-3,4-tetrahydro-β-carboline (**6**).

The synthesis of amine lactam **6** was readily accomplished by two routes, summarized in Scheme I. Treatment of 2-pyrrolidinone (**3**)[8] with sodium hydride in hexamethylphosphoramide–benzene followed by the addition of 3-chloro-1,1-diethoxypropane[8] gave N-(3,3-diethoxypropyl)pyrrolidin-2-one (**4**) as a labile yellow oil in 34% yield. Acid-promoted condensation of lactam acetal **4** with tryptamine (**5**)[8] gave the desired amine lactam **6** in 78% yield. In an alternate route

SCHEME I



to **6**, methanolysis[9] of N-(2-cyanoethyl)pyrrolidin-2-one (**7**)[8] afforded N-(2-carbomethoxyethyl)pyrrolidin-2-one (**8**) in 52% yield. Condensation of lactam ester **8** with tryptamine gave N-[3-oxo-3-(N$_b$-tryptaminyl)-propyl]pyrrolidin-2-one (**9**) in 82% yield. Subsequent treatment of amide lactam **9** with polyphosphate ester (PPE)[10] followed by sodium borohydride gave amine lactam **6** in 40% yield, identical with that prepared by the first route.

With the desired intermediate (**6**) in hand, the task remaining was to construct the sensitive[2] N–C–N portion of elaeocarpidine by a suitable ring closure. As was mentioned earlier, it was believed that lithium aluminum hydride or lithium alkoxyaluminohydride[6] would convert the amide moiety in **6** to the corresponding immonium derivative which would be expected to undergo cyclization[11] to elaeocarpidine (**1**) and/or its

(1) The author wishes to thank the donors of The Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and the Research Corporation for providing generous financial support.

(2) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Chem. Commun.*, 410 (1968).

(3) R. H. F. Manske, Ed., "The Alkaloids," Vol. VIII, Academic Press Inc., New York, N. Y., 1965.

(4) J. Harley-Mason and C. G. Taylor, *Chem. Commun.*, 281 (1969).

(5) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 151 (1951).

(6) For the lithium aluminum hydride reduction of amides to aldehydes, see H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **86**, 1089 (1964).

(7) For the lithium aluminum hydride reduction of oxindoles to indoles, see P. L. Julian and H. C. Printy, *ibid.*, **71**, 3206 (1949).

(8) This material is commercially available from the Aldrich Chemical Co.

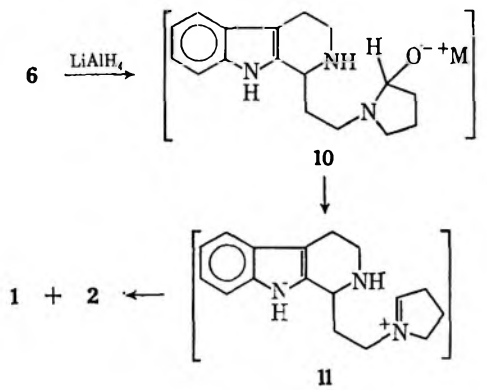
(9) F. L. James and W. H. Bryan, *J. Org. Chem.*, **23**, 1225 (1958).

(10) Y. Kanaoka, E. Sato, and O. Yonemitsu, *Tetrahedron*, **24**, 2591 (1968).

(11) More conventional amide cyclodehydrating reagents seemed unattractive since it was felt that they would preferentially interact with the more nucleophilic secondary amine center in **6**, rather than with the lactam group. Indeed, no cyclization could be detected when **6** was exposed to phosphorus oxychloride, PPE, phosphorus pentoxide, trimethyloxonium fluoroborate, acetic acid, sodium, sodium borohydride, and sodium hydroxide. Similar experiments with amide lactam **9** were unrewarding.

epimer prior to reduction to dihydroelaeocarpidine (**2**). This has been realized and is summarized in Scheme II.[12]

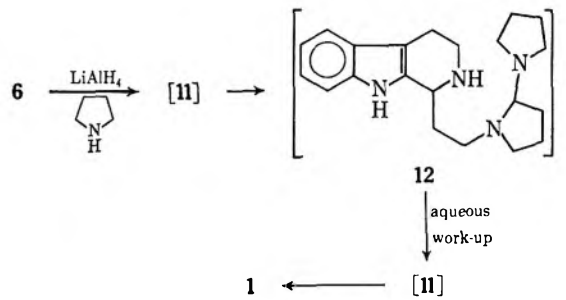
SCHEME II



Treatment of amine lactam **6** with excess lithium aluminum hydride in tetrahydrofuran or diethyl ether at room temperature gave a crystalline reaction product shown to be two compounds by tlc. These could be readily separated by crystallization or column chromatography to give two crystalline compounds. The less soluble compound (30% yield) was found to be completely identical with authentic elaeocarpidine (**1**). The second compound (60% yield) was completely identical with authentic dihydroelaeocarpidine (**2**). Both synthetic specimens gave practically superimposable infrared, ultraviolet, and mass spectra, as well as exhibiting identical tlc behavior with their natural counterparts. A careful search of the reaction mixture using tlc for the unnatural epimer (epielaeocarpidine) was unsuccessful. Even if epielaeocarpidine possessed identical tlc behavior as elaeocarpidine, the complete identity of the infrared spectra of natural with synthetic material, especially in the informative Bohlmann region (2840–2600 cm^{-1}), leaves no doubt that little if any epielaeocarpidine is formed in the cyclization reaction. It must therefore be concluded that elaeocarpidine is formed stereospecifically. Attempts to increase the **1**:**2** ratio by using limited amounts of hydride and/or low temperatures did not significantly alter the original experimental result. Likewise, treatment of amine lactam **6** with lithium diethoxyaluminohydride and lithium triethoxyaluminohydride invariably gave a mixture of **1** and **2**. Control experiments showed no conversion of elaeocarpidine (**1**) to dihydroelaeocarpidine (**2**) under the reaction conditions. Since elaeocarpidine always directly crystallized from the crude reaction product in a nearly pure state, the reductive-cyclization reaction represents a very convenient source of elaeocarpidine. A single crystallization from benzene gave the pure product by tlc.

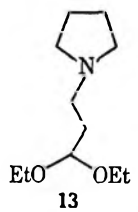
The success of the reductive-cyclization reaction (Scheme II) leading to elaeocarpidine suggested that perhaps the intermediate[13] immonium salt **11** could be more efficiently trapped by an external secondary amine present in large excess.[14] This intermolecular "protection" of the C–N double bond in **11** should prevent overreduction by hydride to dihydroelaeocarpidine (**2**). Aqueous work-up would be expected to regenerate **11** which should cyclize to elaeocarpidine without the interfering presence of lithium aluminum hydride. Indeed, this proposal has been realized and is summarized in Scheme III. Treatment of amine

SCHEME III



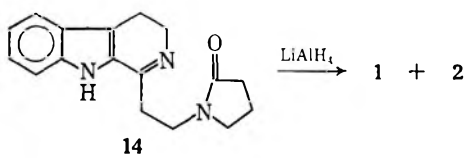
lactam **6** in pyrrolidine–tetrahydrofuran (1:1) at 0° with excess lithium aluminum hydride in small portions over several hours followed by the usual work-up gave elaeocarpidine in 52% yield along with unchanged lactam **6**. More importantly, dihydroelaeocarpidine (**2**) was found to be totally absent from the reaction product.[15]

The structure of dihydroelaeocarpidine (**2**) was further established by independent synthesis. Thus, 3-(N-succinimido)propionaldehyde[16] was converted to N-(3,3-diethoxypropyl)pyrrolidine (**13**) in 29% overall



yield by lithium aluminum hydride reduction of the derived diethyl acetal. Subsequent acid-catalyzed condensation of **13** with tryptamine (**5**) gave dihydroelaeocarpidine (**2**) in 48% yield.

The lithium aluminum hydride reductive cyclization of 1-[2-(2-oxo-N-pyrrolidyl)ethyl]-3,4-dihydro-β-carboline (**14**) was also examined. Imine lactam **14** was readily prepared by treating amide lactam **9** with PPE as previously described but omitting the sodium borohydride reduction step. Treatment of **14** with lithium aluminum hydride gave elaeocarpidine (**1**) and



(12) For simplicity, the acidic hydrogens of **6** are left intact in Scheme II. Probably the indole NH is removed by lithium aluminum hydride and possibly the secondary amine proton is also: J. A. Krynitsky, J. E. Johnson, and H. J. Carhart, *J. Amer. Chem. Soc.*, **70**, 486 (1948).

(13) The intermediate in the cyclization reaction could also be the carbinolamine derivative **10** but, although we as yet have no evidence on this point, we favor a reduction-cyclization competition arising from **11**.

(14) The author is indebted to Professor Heinz G. Viehe for this suggestion.

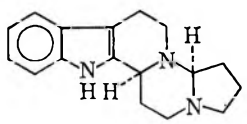
(15) Optimum conditions for this reaction have not been explored as yet, but morpholine behaves similarly. No attempt has yet been made to isolate the intermediate aminal **12**. It seems possible[14] that this reaction (**6** → **12**) may represent a new general enamine synthesis. A study of the scope of this reaction and its implications will be reported separately.

(16) O. A. Moe and D. T. Warner, *J. Amer. Chem. Soc.*, **71**, 1251 (1949).

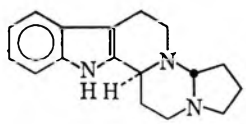
dihydroelaeocarpidine (2) in approximately the same ratio as was obtained from amine lactam **6**. No other compound could be detected by tlc. The structure of **14** was confirmed by its conversion to amine lactam **6** with sodium borohydride in nearly quantitative yield.

Two points remain to be settled: the reason for the stereospecificity of the reductive cyclization of amine lactam **6** and the stereochemistry of elaeocarpidine.

An examination of Dreiding models of immonium salt **11**, the presumed intermediate in the reductive-cyclization reaction, reveals that if attack occurs by the piperidine nitrogen from an equatorial position it will occur on the top face (as drawn in **11**) of the immonium derivative leading to a *cis* arrangement of methine hydrogens in elaeocarpidine (**1a**). The equatorial nucleophile can come very close to the electrophilic carbon atom without evident strain or other interactions. On the other hand, if attack occurs *via* the axial position of the piperidine nitrogen, models predict that it will occur on the bottom face of the five-membered ring leading to a *trans* arrangement of methine hydrogens in elaeocarpidine (**1b**). Thus, it appears from



1a

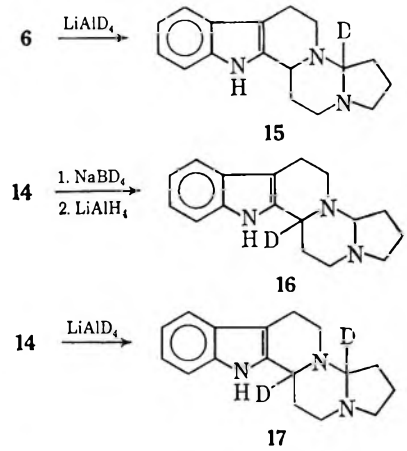


1b

these arguments[17] that the stereospecificity of the ring closure can be rationalized, but, because the attacking conformation of the piperidine ring is unknown, the stereochemistry of elaeocarpidine cannot be predicted with certainty.

Stereochemistry.—For each of the two possible configurations of elaeocarpidine (**1a** or **1b**) there are several conformations available due to nitrogen inversion and ring flipping in the molecule.[18] To establish which conformation(s), and hence configuration, exists for elaeocarpidine, an examination of the nmr and infrared spectra of elaeocarpidine and the deuterated elaeocarpidines **15**, **16**, and **17** was made. The preparation of **15**, **16**, and **17** is outlined. The structure of each deuterated alkaloid follows directly from the method of preparation, from spectral and tlc comparison with undeuterated elaeocarpidine, and from mass spectral data.

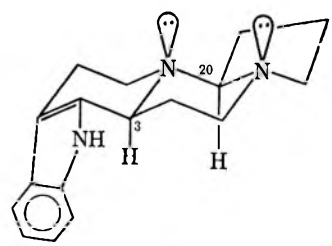
The infrared spectrum of elaeocarpidine (**1**) shows several intense bands in the 2845–2660-cm^{-1} region commonly known as Bohlmann bands,[19] which are characteristic of conformations having two or more protons in a 1,2-*trans*-diaxial arrangement with a nitrogen lone pair. The infrared spectra of **15**, **16**, and **17**



also show intense Bohlmann bands in the 2800–2700-cm^{-1} region. These observations strongly imply that at least the lone pair on N_c is flanked by two protons in a *trans*-diaxial arrangement. The conformations which satisfy this criterion are the *trans-anti-trans* (**1a**), the *cis-syn-trans* (**1a**), and the *cis-anti-trans* (**1b**).[20]

The infrared spectra of the deuterated elaeocarpidines is also informative in the C–D stretching region. Compound **15** shows a band at 1930 cm^{-1}, **16** shows a band at 1990 cm^{-1}, and **17** shows two bands, at 1990 and 1935 cm^{-1}. Since it is established[19] that C–D bonds that are 1,2 *cis* to a nitrogen lone pair appear at higher frequency than those that are 1,2 *trans* diaxial (~2150 *vs.* 2000 cm^{-1} for methylene and methine groups), it is very tempting to conclude that the C_7–H(D) and C_{20}–H(D) bonds in **15**, **16**, and **17** (and by analogy **1**) are *trans*-diaxially situated to the nitrogen lone pairs. Furthermore, the unusually low frequency value of 1930 cm^{-1} for **15** is fully consistent with the $C_{20}D(H)$ being *trans* diaxial to both nitrogen lone pairs, resulting in a very efficient interaction.[19,21] The only conformation which has $C_{20}H$ *trans* diaxial to both lone pairs and C_7H *trans* diaxial to one lone pair is the *trans-anti-trans* (**18**).

An nmr examination of elaeocarpidine (**1**) likewise supports the *trans-anti-trans* conformation (*cis* con-



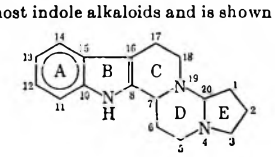
18 (1a)

figuration) arrived at from infrared-based conclusions.

The 60-MHz nmr spectrum of elaeocarpidine in $DCCl_3$ shows no saturated C–H absorption below 3.5 ppm. Similarly, at 100 MHz no methylene or methine absorption appears downfield from the main saturated C–H absorption band. This observation supports the infrared-based conclusion that the C_7H in **1** is *trans* to the adjacent nitrogen lone pair. This follows since

(17) Similar considerations have led to an elegant structure proof and synthesis of cernuine and related lycopodium alkaloids: W. A. Ayer and K. Piers, *Can. J. Chem.*, **45**, 451 (1967), and accompanying papers.

(18) The numbering system used for elaeocarpidine follows the general system adopted for most indole alkaloids and is shown in i.



i

(19) J. Skolik, P. J. Krueger, and M. Wiewiorowski, *Tetrahedron*, **24**, 5439 (1968), and references therein.

(20) The *trans-syn-trans* conformation, having a boat D ring, would not show intense Bohlmann bands.

(21) (a) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964); (b) M. J. T. Robinson, *ibid.*, 1153 (1968).

it is well established that when a 1,2-*cis* proton lone-pair relationship exists, the absorption for this proton appears at very low field (3.6–4.5 ppm) relative to the 1,2-*trans* diaxial arrangement (1.7–3.2 ppm) in indolo[2,3-*a*]quinolizidines.[22,23]

In summary, on the basis of infrared and nmr evidence, it must be concluded that the preferred conformation of elaeocarpidine (**1**) is *trans-anti-trans* (**18**) and, therefore, **1** exists as the *cis* configuration **1a**.

Chemical observations also tend to support the more stable *cis* configuration for **1**, although in a negative sense. Attempts to epimerize **1** to epielaeocarpidine (**1b**) using sodium methoxide–methanol, potassium *t*-butoxide–hexamethylphosphoramide, pivalic acid–toluene, hydrobromic acid–acetic acid, and *p*-toluenesulfonic acid–benzene–ethanol were uniformly unsuccessful and led to recovered elaeocarpidine and, in some cases, dihydroelaeocarpidine and amine lactam **6**. Similarly, oxidation of elaeocarpidine with mercuric acetate followed by reduction with sodium borohydride or zinc gave no epielaeocarpidine as judged by tlc.

Finally, studies on other ring systems tend to support the stereochemistry for elaeocarpidine arrived at in the present paper. Quinolizidine and indolizidine both predominate with the *trans* ring fusion having free energy differences of 2.1–4.4 and 1.9 kcal/mol, respectively.[24] In contrast, the pyrrolizidine system exists in the *cis*-fused form since the *trans* is appreciably strained.[25]

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 137 or 337 instruments. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Unless otherwise stated, proton magnetic resonance spectra were recorded on a Varian HA60-IL spectrometer using tetramethylsilane as an internal standard. Woelm alumina was used for column chromatography and silica gel G was used for thin layer chromatography. The tlc solvent system found to be most satisfactory was methanol–triethylamine (~95:5). Other solvent systems used, when comparing authentic material with synthetic material, were ethyl acetate–triethylamine (~95:5), methylene chloride–triethylamine (~95:5), and chloroform–methanol (~90:10). The developing agent was 3% ceric sulfate–10% sulfuric acid solution which was followed by a 5-min heat treatment at 102°. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

N-(3,3-Diethoxypropyl)pyrrolidin-2-one (4).—To a suspension of 11.5 g (56.8%, 0.27 mol) of sodium hydride, which had been washed several times with dry light petroleum ether to remove the mineral oil coat, in 400 ml of dry benzene and 800 ml of dry hexamethylphosphoramide under nitrogen at 25° was added dropwise 22.9 g (0.27 mol) of 2-pyrrolidinone[8] (**3**) with stirring. The mixture was then heated at 70° for 0.5 hr. After cooling the mixture to 5–10°, 45 g (0.27 mol) of 3-chloro-1,1-diethoxypropane[8] was added over a 0.5-hr period. After standing overnight (10 hr) the mixture was refluxed for 1 hr. Stirring under nitrogen was maintained throughout all of these operations. Most of the solvent was removed *in vacuo* and the remaining mixture was poured onto ice water and extracted with benzene. The organic layer was washed with cold distilled water, dried (Na_2SO_4), and concentrated *in vacuo* to give 20 g (34%) of a yellow oil. This material slowly darkened on standing and was used immediately after preparation, without further purification.

Pertinent spectral data for **4** are as follows: ir ($CHCl_3$) 2990, 1678, 1494, 1462, 1441, 1421, 1288, 1261, 1123, 1053 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (t, 6, J = 7 Hz), 2.00 (m, 6), 3.49 (m, 8), and 4.48 (t, 1, J = 5.5 Hz).

N-(2-Carbomethoxyethyl)pyrrolidin-2-one (8).—This was prepared using a slightly modified procedure of James and Bryan.[9] A mixture of 50 g (0.361 mol) of N-(2-cyanoethyl)pyrrolidin-2-one[8] (**7**), 68.8 g (0.361 mol) of *p*-toluenesulfonic acid monohydrate, and 115 g (3.6 mol) of methanol was stirred at reflux for 20 hr. A precipitate of presumably ammonium *p*-toluenesulfonate forms after 3 hr. During the final stage of reflux 125 ml of methanol was removed by distillation. To the cooled reaction mixture was added water and then solid sodium carbonate until the mixture was slightly basic. This was extracted with chloroform, which was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a red oil. Distillation under reduced pressure gave 32.3 g (52%) of **8** as a colorless oil, bp 102–104° (0.2 mm).

Pertinent spectral data for **8** are as follows: ir ($CHCl_3$) 2980, 1730, 1669, 1483, 1450, 1426, 1412, and 1282 cm^{-1}; nmr ($CDCl_3$) δ 2.28 (m, 6), 3.51 (m, 4), and 3.68 (s, 3); mass spectra (70 eV) *m/e* 171, 138 (nitrile impurity), 112, 111, 98, 84, 70, 56, 55, 54, 42, and 41.

1-[2-(2-Oxo-N-pyrrolidyl)ethyl]-1,2,3,4-tetrahydro-β-carboline (6).—A mixture of 23 g (0.117 mol) of tryptamine hydrochloride[8] (**5**), 25.2 g (0.117 mol) of lactam acetal **4**, and 200 ml of water was refluxed for 1 hr under nitrogen with stirring. At this time an additional 0.117 mol of hydrochloric acid (10 ml of 12 *N* HCl–20 ml of water) was added and heating continued for 0.5 hr. The dark amber solution was allowed to cool, washed with ether (discarded), made basic with aqueous sodium hydroxide, and extracted with chloroform–methanol. The organic layer was washed with water, dried (K_2CO_3), and concentrated *in vacuo* to give 38 g of an amber foam. Chromatography over activity III basic alumina gave, with benzene–chloroform elution, 25.9 g (78%) of a viscous yellow syrup which slowly crystallized on standing. Tlc showed one major spot (90%) and several tiny impurity spots. Crystallization from methylene chloride–ether gave tiny colorless crystals of **6**, mp 132–134°.

Pertinent spectral data for **6** are as follows: ir ($CHCl_3$) 3550, 3310, 2960, 1670, 1494, 1467, and 1452 cm^{-1}; mass spectra (70 eV) *m/e* 283, 197, 185, and 171. *Anal.* Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found: C, 71.76; H, 7.49; N, 14.98.

N-[3-Oxo-3-(N$_b$-tryptaminyl)propyl]pyrrolidin-2-one (9).—A mixture of 4.0 g (0.025 mol) of tryptamine (**5**) and 4.28 g (0.025 mol) of **8** was heated with stirring under nitrogen at 130–160° for 1 hr and at 160–170° for 5 hr. The reaction can be conveniently followed by tlc. The amber red syrup was allowed to cool to about 50°, diluted with benzene, and chromatographed over activity III neutral alumina. Elution with benzene–chloroform (increasing concentrations of the latter) gave a yellow syrup which crystallized on standing. Crystallization from methanol–ether gave 3.64 g (49%) (two crops) of **9** as tiny needles, mp 118–119°. The mother liquors could be rechromatographed to give additional pure material as judged by tlc.

In subsequent preparations of **9** the crude reaction mixture was diluted with methanol and ether, seeded with pure **9**, and allowed to stand at 5°. In this fashion there was obtained directly pure **9** in 66% yield. An additional 16% could be obtained by chromatography of the mother liquors.

Pertinent spectral data for **9** are as follows: ir ($CHCl_3$) 3590, 3370, 3030, 1671, 1517, 1481, and 1285 cm^{-1}; mass spectra (70 eV) *m/e* 299, 157, 144, 143, 140, 130, and 98. *Anal.* Calcd for $C_{17}H_{21}N_3O_2$: C, 68.21; H, 7.07; N, 14.04. Found: C, 68.35; H, 7.05; N, 14.08.

Amine Lactam 6 from Amide Lactam 9.—A mixture of 1.3 g (4.35 mmol) of amide lactam **9** and 6 g of polyphosphate ester (PPE) in 15 ml of dry chloroform was refluxed under nitrogen with stirring for 4.5 hr then at room temperature for 8 hr. The dark green mixture was poured into water, made basic with 10% sodium carbonate solution, diluted with ethanol, and treated with 5 g of sodium borohydride at 0° for 1 hr and 25° for 20 hr. Ether extraction gave, after water washing, drying (K_2CO_3), and concentration *in vacuo*, 0.72 g of a yellow-orange foam. Chro-

(22) (a) W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.*, **83**, 4816 (1961); (b) E. Wenkert, B. Wickberg, and C. L. Leicht, *ibid.*, **83**, 5037 (1961); (c) E. Wenkert and B. Wickberg, *ibid.*, **84**, 4914 (1962); (d) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963); (e) H. Zinnes, R. A. Comes, and S. Shavel, Jr., *ibid.*, **30**, 105 (1965); and (f) C. M. Lee, W. F. Trager, and A. H. Beckett, *Tetrahedron*, **23**, 375 (1967).

(23) Conformations having $C_{20}H$ *cis* to both of the lone pairs can also be excluded since the proton absorption would also be at low fields (below 3.5 ppm). This is especially significant since models indicate that the *trans-syn-cis* conformation would appear to be the most favorable one for the *trans*-configuration **1b**.

(24) H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, 6191 (1968).

(25) I. M. Skvortsov and J. A. Elvidge, *J. Chem. Soc., B*, 1589 (1968).

matography over activity III basic alumina gave, with benzene–chloroform elution, 0.51 g (41%) of **6** as a yellow oil which slowly crystallized. This material was identical (infrared, tlc behavior) with that obtained earlier.

Elaeocarpidine (1) and Dihydroelaeocarpidine (2).—To a solution of 4.2 g (14.8 mmol) of amine lactam **6** in 140 ml of dry tetrahydrofuran at 0° under nitrogen with stirring was added in one portion 1.5 g (40 mmol) of lithium aluminum hydride. The mixture was stirred at 0° for 1 hr, then at 25° for 18 hr. To the ice-cold mixture was added successively ice water (dropwise), 6 *N* sodium hydroxide, water, and ether. The organic extract was washed with water, dried (K_2CO_3), and concentrated *in vacuo* to give 4.0 g of a yellow syrup which partially crystallized. Trituration with hot benzene and collection of the resulting white solid afforded 0.675 g (17%) of nearly pure elaeocarpidine contaminated with only a small amount of dihydroelaeocarpidine as indicated by tlc. Crystallization from benzene–methanol gave pure elaeocarpidine, mp 226–227° (slight sintering and darkening at 222°). This synthetic material was completely identical with authentic elaeocarpidine [infrared, mass spectral analysis, tlc (four solvent systems: spot shape, color, and mobility as well as spot enhancement), and ultraviolet]. The unnatural epimer could not be detected by tlc in either the synthetic or natural elaeocarpidine.

On standing, the mother liquor from above deposited 1.19 g (30%) of practically pure dihydroelaeocarpidine, mp 119–122°, which was contaminated with but a trace (tlc) of elaeocarpidine. Crystallization from methanol–ether gave pure dihydroelaeocarpidine, mp 123–124°. This material was identical with authentic dihydroelaeocarpidine (by same criteria used to compare elaeocarpidine).

Chromatography of the mother liquors from above over activity III "super 200" basic alumina gave, with benzene–chloroform elution (increasing concentrations of the latter), 1.25 g (31%) of dihydroelaeocarpidine (pure by tlc) and 0.39 g (10%) of elaeocarpidine, slightly contaminated (tlc) by a small amount of dihydroelaeocarpidine.

Pertinent spectral data for these compounds are as follows.

Elaeocarpidine: ir ($CHCl_3$) 3525, 2950, 2845, 1450, 1372, 1356, 1300, and 1170 cm^{-1}; mass spectrum (70 eV) *m/e* 267, 266, 239, 225, and 160. *Anal.* Calcd for $C_{17}H_{21}N_3$: C, 76.37; H, 7.92; N, 15.72. Found: C, 76.50; H, 7.86; N, 15.86.

Dihydroelaeocarpidine: ir ($CHCl_3$) 3535, 2940, 2835, 1492, and 1448 cm^{-1}; mass spectrum (70 eV) *m/e* 269, 239, 225, 198, 185, 184, and 171. *Anal.* Calcd for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N, 15.60. Found: C, 75.86; H, 8.66; N, 15.83.

Treatment of 1 with Lithium Aluminum Hydride.—A mixture of elaeocarpidine (**1**) and dihydroelaeocarpidine (**2**) (0.70 g; ~50:50) was refluxed with lithium aluminum hydride (0.10 g) in tetrahydrofuran under nitrogen. Aliquots were periodically removed, processed, and examined by tlc. No change in the 1/2 ratio was observed. After 15 hr the reaction mixture was worked up to give 0.5 g of product which showed the same elaeocarpidine/dihydroelaeocarpidine ratio as was present at the beginning of the reaction. No other spots were present on the tlc chromatogram.

Elaeocarpidine (1) from 6 in the Presence of Pyrrolidine.—To a solution of 2.25 g of amine lactam **6** in 50 ml of dry tetrahydrofuran and 50 ml of dry pyrrolidine under nitrogen at 0° was added 2 g of lithium aluminum hydride in spatula-tip portions over 10 hr. The usual work-up gave 1.1 g (52%) of nearly pure elaeocarpidine (tlc) contaminated with a small amount of **6**. No dihydroelaeocarpidine (**2**) could be detected by tlc.

N-(3,3-Diethoxypropyl)pyrrolidine (13).—A mixture of 33 g (0.201 mol) of 3-(N-succinimido)propionaldehyde, 150 ml of dry ethanol, 5 g of anhydrous calcium chloride, and 6 drops of concentrated hydrochloric acid was allowed to stand at 25° for 5.5 days. Fresh calcium chloride was added periodically so that it was always present in solid form. The mixture was made slightly basic with sodium ethoxide and the ethanol was removed *in vacuo*. The solid residue was added in portions to a suspension of 40 g of lithium aluminum hydride in 1 l. of dry tetrahydrofuran. After addition, the mixture was refluxed under nitrogen for 24 hr. The excess lithium aluminum hydride was destroyed by cautious addition of ice water to the ice-cold reaction mixture. This was followed by the addition of 6 *N* sodium hydroxide and extraction with ether. The organic layer was washed with cold distilled water, dried (K_2CO_3), and concentrated *in vacuo* to give 13 g of a yellow oil. Distillation under reduced pressure gave 11.7 g (29%) of pure **13** as a colorless oil, bp 101–103° (8–9 mm).

Pertinent spectral data for **13** are as follows: nmr ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz), 1.82 (m, 6), 2.50 (m, 6), 3.57 (m, 4), and 4.57 ppm (t, 1, J = 5.5 Hz); ir ($CHCl_3$) 2940, 1450, 1388, 1368, and 1344 cm^{-1}; mass spectrum (70 eV) *m/e* 201, 172, 157, 128, 126, 98, 84, 70, 57, 55, and 42. *Anal.* Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.44; H, 11.39; N, 7.07.

Dihydroelaeocarpidine (2) from Amine Acetal 13. To a mixture of 9.75 g (0.0496 mol) of tryptamine hydrochloride in 50 ml of water at 75° under nitrogen with stirring was added dropwise 9.9 g (0.0493 mol) of **13**. The mixture was heated at 80–90° for 0.5 hr, an additional 0.049 mol of hydrochloric acid (4 ml of 12 *N* HCl) was added, and the mixture was refluxed for an additional 1 hr. The cooled mixture was filtered and the residue was washed with aqueous hydrochloric acid. The combined acid extract was washed with ether (discarded), made basic with aqueous sodium hydroxide, and extracted with chloroform. This afforded after the usual manipulation 10.2 g (77%) of an amber syrup. Chromatography over activity III basic alumina gave, with benzene–chloroform elution, 6.3 g (48%) of dihydroelaeocarpidine (**2**) as an oil which slowly crystallized (nearly pure by tlc). Crystallization from methanol–ether–petroleum ether (bp 20–40°) gave prism clusters, mp 123–124°. This material was identical with that obtained by lithium aluminum hydride reduction of lactam acetal **6** as well as with authentic material (infrared and tlc behavior).

1-[2-(2-Oxo-N-pyrrolidyl)ethyl]-3,4-dihydro-β-carboline (14).—A mixture of 5.1 g (17 mmol) of amide lactam **9**, 25 g of PPE, and 60 ml of dry chloroform was refluxed under nitrogen for 4 hr. The dark mixture was poured into water, made basic with sodium hydroxide, and extracted with methylene chloride. This afforded 1.37 g of an amber foam showing on tlc a spot different from amine lactam **6** and amide lactam **9**. Chromatography over activity III neutral alumina gave, with benzene–chloroform elution, 0.5 g (10%) of **14**, mp 145–148°, showing the expected long-wavelength uv absorption at 236 and 316 mμ. This material (pure by tlc) was used directly in the reductive cyclization.

Interestingly, sodium borohydride reduction of the aqueous basic layer gave 2 g (41%) of amine lactam **6**, indicating incomplete extraction of **14** into the organic layer.

Pertinent spectral data for **14** are as follows: ir ($CHCl_3$) 3260, 2960, 1667, 1629, 1550, 1495, 1470, 1448, 1317, and 1288 cm^{-1}.

Imine lactam **14** could not be satisfactorily crystallized and was characterized by sodium borohydride reduction to **6** in quantitative yield.

Preparation of 15.—A mixture of 0.9 g of amine lactam **6**, 0.35 g of lithium aluminum deuteride, and 35 ml of dry tetrahydrofuran was stirred under N_2 for 30 min at 0°, 5 hr at 25°, and 1 hr at reflux. The usual work-up gave 0.64 g of an oil which crystallized on standing. Tlc showed two spots of equal intensity having same characteristics as **1** and **2**. A single crystallization from benzene gave pure (tlc) **15**, mp 214–222°.

Pertinent spectral data for **15** are as follows: ir ($CHCl_3$) 3525, 2945, 2845, 2790, 2731, 1930, 1449, 1373, 1296, 1279, and 1177 cm^{-1}; mass spectrum (70 eV) *m/e* 268, 240, 226, and 171.

Preparation of 16.—A mixture of 3.3 g of imine lactam **14**, 1 g of sodium borodeuteride, and 50 ml of methanol-O-*d* was stirred at 0° for 1 hr and then at 25° for 15 hr. The solution was diluted with water and extracted with methylene chloride. The usual manipulation gave 3.3 g of an amber foam. This was treated directly in the usual fashion with 1 g of lithium aluminum hydride in 60 ml of dry tetrahydrofuran at 0° for 30 min, at 25° for 18 hr, and at reflux for 1 hr. Work-up gave a yellow oil which crystallized slowly. Tlc showed two spots having the same characteristics as **1** and **2**. Crystallization from benzene afforded pure (tlc) **16**, mp 222–225°.

Pertinent spectral data for **16** are as follows: ir ($CHCl_3$) 3490, 2935, 2845, 2795, 2730, 1990, 1449, 1352, 1290, and 1267 cm^{-1}; mass spectrum (70 eV) *m/e* 268, 241, 240, 227, and 226.

Preparation of 17.—A mixture of 1.3 g of imine lactam **14**, 0.53 g of lithium aluminum deuteride, and 50 ml of dry tetrahydrofuran was stirred under nitrogen for 1 hr at 0°, 5 hr at 25°, and 3 hr at reflux. The usual work-up gave 1.1 g of an amber oil which crystallized on standing. Tlc showed two spots having the same characteristics as **1** and **2**. A single crystallization from benzene gave pure (tlc) **17**, mp 221–225°.

Pertinent spectral data for **17** are as follows: ir ($CHCl_3$) 3525, 2950, 2845, 2795, 2725, 1990, 1935, 1457, 1370, 1326, 1298, 1282, 1163, and 1124 cm^{-1}; mass spectrum (70 eV) *m/e* 269, 241, and 227.

Registry No.—**1**, 24343-81-5; **2**, 24298-76-8; **4**, 24299-76-1; **6**, 24298-77-9; **8**, 24299-77-2; **9**, 24343-82-6; **13**, 24299-78-3 **14**, 24299-79-4; **15**, 24298-78-0; **16**, 24298-79-1; **17**, 24343-83-7.

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4-Carbomethoxy-5α-androstane Derivatives. Synthesis of (−)-Sandaracopimaric Acid

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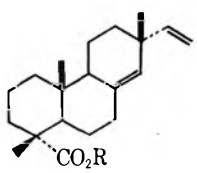
Received November 21, 1969

Novel steroidal β-keto esters **4** and **6** were prepared by direct carbonation of 17β-acetoxy-5α-androst-1-en-3-one (**3**) or by the reductive carbomethoxylation of testosterone acetate, respectively. Methylation of **6** affords selectively **7**, the expected product of stereoelectronically controlled axial alkylation. A reversal in the predicted stereochemical course of alkylation was observed with **4**, which afforded **11** as its exclusive methylation product. The configurations at C-4 in **7** and **11** were established through the corresponding 3-deoxy esters **9** and **10**. Ester **9** was converted by a series of reactions into (−)-sandaracopimaric acid (**1**).

Considerable support for the stereochemistry of the isomeric pimaric acids was provided by the syntheses of racemic pimaradiene and sandaracopimaradiene.[1] The stereochemical ambiguity at C-13[2] of the synthetic hydrocarbons was subsequently resolved by the conversion of testosterone into (−)-sandaracopimaradiene by three independent routes.[3] The synthesis of a pimaric acid-type natural product possessing a carboxyl group at C-4, however, has not been described in the literature. In this paper[4] we report the first synthesis of (−)-sandaracopimaric acid[5] (**1**) a diterpenoid resin acid isolated from *Callitris quadrivalvis*, starting from testosterone acetate. The present work provides a direct confirmation of the assigned structure **1** and absolute stereochemistry for the natural acid.



1, R = H
2, R = CH_3

Sandaracopimaric acid (**1**) has the same absolute stereochemistry at carbons 5, 9, 10, and 13 as steroids of the 5α series. Hence, the only stereochemical prerequisite for the conversion of a 5α steroid into **1** is the construction of the abietic acid type[6] of substitution pattern at C-4 of the steroid. Such a substitution pattern or the epimeric podocarpic acid type[6] of arrangement has been attained by a variety of approaches[7] in the syntheses of other resin acids from bi- and tricyclic intermediates. Among these approaches, the most direct method has been the selective methylation of β-keto esters.[8−10] We utilized this approach in preparing the epimeric keto esters **7** and **8**. Our interest in this area evolved from a program involving the preparation of novel 4-substituted androstane and pregnane derivatives for biological studies.

4-Carbomethoxy-5α-androstanes.—By analogy with the tricyclic series,[8] keto esters **4** and **6** would be the substrates of choice since methylation of either of these compounds would be expected to proceed by β attack, thereby providing the desired abietic acid type[6] of stereochemistry at C-4. Two methods were used for the introduction of the carbomethoxy group at C-4 of the appropriate steroid substrate. Using the direct carbonation procedure,[11,12] 17β-acetoxy-5α-androst-1-en-3-one[13] (**3**) was treated with an excess of tritylsodium followed by the introduction of carbon dioxide and conversion of the resulting acid into its methyl ester by reaction with diazomethane. Tlc indicated that the product was a complex mixture of keto esters and starting enone **3** in which the 17-acetate group had partially hydrolyzed and also had partially undergone carbona-

(1) (a) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963); (b) for a review, see R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965).

(2) Diterpene numbering as in ref 1b. This numbering will also be used for steroidal derivatives that do not contain C-15.

(3) (a) A. K. Bose and S. Harrison, *Chem. Ind.* (London), 1307 (1961); (b) M. Fetizon and M. Golfier, *Bull. Soc. Chim. Fr.*, 167 (1963); (c) P. Johnston, R. C. Sheppard, C. E. Stehr, and S. Turner, *J. Chem. Soc., C*, 1847 (1966).

(4) A preliminary report on this work has been published: A. Afonso, *J. Amer. Chem. Soc.*, **90**, 7375 (1968).

(5) (a) O. E. Edwards, A. Nicholson, and M. N. Rodger, *Can. J. Chem.*, **38**, 663 (1960); (b) V. Galik, J. Kulhan, and F. Petru, *Chem. Ind.* (London), 722 (1960); (c) A. K. Bose, *ibid.*, 1104 (1960).

(6) The term "abietic acid type" is used herein to denote an asymmetric center containing a β-methyl and an α-carboxyl group. "Podocarpic acid type" denotes the alternative arrangement (α-methyl, β-carboxyl).

(7) *Cf.* citations in ref 8–10.

(8) E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *J. Amer. Chem. Soc.*, **86**, 2038 (1964), and earlier papers cited.

(9) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

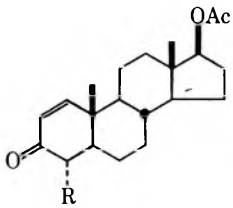
(10) T. A. Spencer, R. J. Friary, W. W. Schniegel, J. F. Simeone, and D. S. Watt, *ibid.*, **33**, 719 (1968).

(11) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

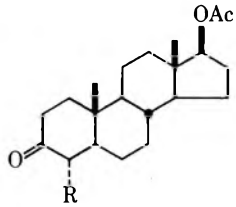
(12) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **81**, 5601 (1959).

(13) R. E. Counsell, P. D. Klimstra, and F. B. Cotton, *J. Org. Chem.*, **27**, 248 (1962).

tion. The crude reaction product was subjected to a selective hydrolysis of the 17-ester functions under acidic conditions, followed by acetylation. The product resulting from this treatment was predominantly a mixture of **3** and **4** and upon chromatography afforded the desired 4α-carbomethoxy-17β-acetoxy-5α-androst-1-en-3-one (**4**) in 30% yield. Catalytic reduc-



3, R = H
4, R = $-CO_2CH_3$

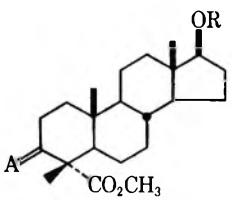


5, R = H
6, R = $-CO_2CH_3$

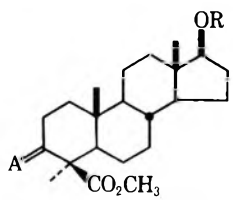
tion of **4** led to the formation of **6**. Alternatively, **6** was prepared by using Stork's procedure[14] for reductive carbomethoxylation.[9] Thus, testosterone acetate was treated with lithium in ammonia followed by carbon dioxide and, upon acidification, treated with diazomethane followed by acetylation. Chromatography of the reaction product resulting from this sequential treatment afforded 4α-carbomethoxy-17β-acetoxy-5α-androstan-3-one (**6**) in 24% yield. From the same reaction 17β-acetoxy-5α-androstan-3-one (**5**) was also isolated. No carbonation at C-2, which would result from equilibration of the C-4 anion,[9] was detectable in the reaction product.

In the nmr, the 4β-proton resonance of both **4** and **6** appears as a doublet with an axial–axial coupling of 12.5 cps. As has been observed in other *trans*-fused 4-carbalkoxy-3-ones,[9,12] neither of the keto esters **4** or **6** exhibits spectral properties of an enolized β-keto ester.

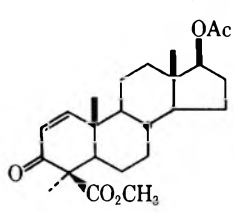
The keto esters **4** and **6** were alkylated with methyl iodide in benzene using sodium hydride as the base. Methylation of **6** proceeded selectively to afford **7** as the major product. From the same alkylation, a small yield of the epimeric compound **8** was also isolated, the ratio of **7** to **8** being 9.2:0.8. Under the same condi-



7, A = O; R = CH_3CO-
9, A = H_2; R = H



8, A = O; R = CH_3CO-
10, A = H_2; R = H



11

tions, the methylation of **4** was stereospecific, **11** being the only alkylated product formed in the reaction. Catalytic reduction of **11** afforded **8**, the minor methylation product of **6**.

(14) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965).

The nmr spectrum of **8** shows a sextet (J = 14.5, 14.5, and 6 cps) with an intensity of 1 H centered at δ 2.93. It is noteworthy that this resonance, assigned to the 2β proton of **8**, is absent in **7** and **10**. Large values for J_{aa} and J_{ae} such as the ones above, observed for **8**, are not unusual.[15] The downfield position of the chemical shift of the 2β proton of **8** is interpreted as indicative of a chair conformation for ring A, wherein the carbonyl of the ester group can exert a deshielding effect on the 2β proton. Similar deshielding effects on protons held in the plane of a carbonyl group have been observed.[16]

Clemmensen reduction of the methylated keto esters **7** and **8** afforded the epimeric 3-deoxy esters **9** and **10**, respectively. A comparison of the relative susceptibility of the esters to basic hydrolysis showed that **10** is resistant to hydrolysis while **9** is not. In agreement with the hydrolytic data, the 19-methyl proton resonance of **10** appears at δ 0.70 shielded[17] by 0.19 ppm relative to the corresponding resonance of **9** at δ 0.89. The 1,3-diaxial shielding by a carbonyl group has been used as a diagnostic test to distinguish between analogous C-4 stereoisomers in other series.[9,18] The above hydrolytic and nmr data established unequivocally the stereochemistry at C-4 in compounds **9** and **10** and hence in **7**, **8**, and **11**.

Stereochemistry of Alkylation.—As expected,[8] the methylation of **6** proceeds selectively to afford **7**, the product of stereoelectronically controlled alkylation (axial attack by the alkylating agent). The stereochemical course of the methylation of **4**, however, is opposite (exclusive α attack by the alkylating agent to form **11**) to that observed in analogous substrates.[19] Examination of Dreiding models of **4** and **6** does not reveal overwhelming differences, in either the steric shielding due to the angular group or in *peri* interactions between C-4, C-6 and C-11, C-1 that would account for the impressive reversal of the stereochemical course of alkylation of **4**. It is obvious that extraordinarily subtle factors in **4** affect the approach of the alkylating agent. Exclusive α-methylation of **4** can be regarded to be stereoelectronically controlled if ring A acquires a boat conformation in the transition state of its alkylation. Dreiding models indicate that twisting of ring A, which is easier in **4** than in **6**, somewhat relieves the *peri* interactions.

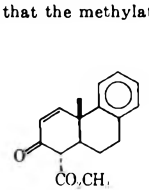
(15) (a) S. G. Levine and R. E. Hicks, *Tetrahedron Lett.*, 5409 (1968), and citation 9 therein; (b) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).

(16) D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2810 (1963).

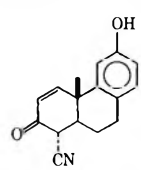
(17) The magnitude of the shielding effect in the corresponding 3-keto compound **8** is much reduced (0.06 ppm) relative to **10**.

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

(19) The methylation of the analogous keto ester i, in contrast to that of **4**, proceeds by attack of the alkylating agent from the β side exclusively.[8] It is noteworthy that the methylation of the related substrate ii, originally



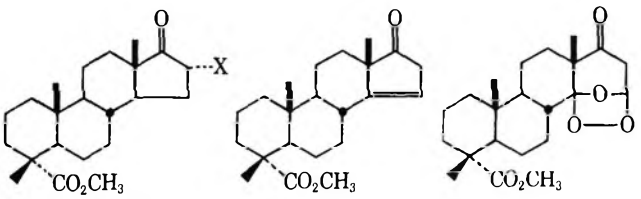
i



ii

reported to following the same stereochemical course as i [M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961)], has now been reinvestigated and found to proceed from the α side [M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35**, 161 (1970)].

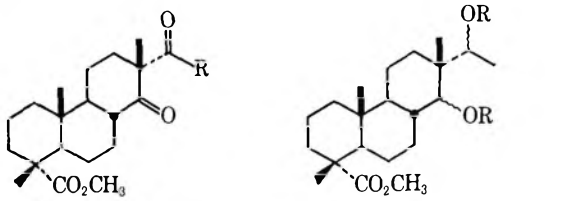
Cleavage of Ring D.—With the conclusion of the construction of the desired substitution pattern at C-4 as in ester **9**, formation of an olefinic bond at C-14(15) in **9** was necessary in order to carry out subsequent steps to cleave ring D. In the described conversions of steroidal derivatives into sandaracopimaradiene, this objective was achieved by the acid-catalyzed migration of a 5,6 olefinic bond[3b,c] or through a 16-benzylidene derivative.[3a] Our approach is based on the observation that steroidal 16-α-bromo-17-ones, on dehydrobromination with lithium bromide–lithium carbonate in dimethylformamide, afford the corresponding 14(15)-en-17-ones in reasonable yield.[20] Thus, Jones oxidation of **9** gave the 17-ketone **12** which was converted into the corresponding enol acetate by refluxing with isopropenyl acetate in the presence of *p*-toluenesulfonic acid. The enol acetate without further purification



12, X = H
13, X = −Br

14

15



16, R = −CH═CHOH
17, R = −CH(S)(S)
18, R = −CH_3

19, R = H
20, R = C_6H_5CO−

was treated with bromine to afford the 16α-bromo derivative **13**. The configuration of the bromo group is based on analogies.[21] Dehydrobromination of **13**, under the conditions mentioned earlier, afforded the 4β-methyl-4α-carbomethoxy-5α-androst-14-en-17-one (**14**) in 32% yield. The product does not absorb in the uv and its nmr spectrum shows the presence of one vinyl proton. Ozonization of **14** at low temperature led to the formation of a stable crystalline ozonide **15**. In the nmr, the protons at C-15 and C-16 of **15** show an ABX splitting pattern. Originally it was hoped that ozonization of **14** followed by oxidative work-up would afford a β-keto acid which would readily decarboxylate to form the diketone **18**. However, attempted oxidative work-up of the ozonization product by the conventional procedures led to the recovery of starting material. Reductive work-up using zinc–acetic acid was equally unsuccessful; however, catalytic hydrogenolysis of **15** in the presence of palladized carbon proceeded at a rapid rate, with the consumption of 1 equiv of hydrogen, to afford the hydroxymethylene derivative **16**. In agreement with structure **16**, the product gives a positive ferric chloride test and its absorption maximum undergoes the characteristic bathochromic shift in alkaline solution.[22] Decarbonylation of **16** using ethylene *p*-toluenethiolsulfonate,[23] proceeded smoothly to yield the thioketal **17**. This decarbonylation procedure was used in order to circumvent bond cleavages which could occur between carbons 13 and 14 or 13 and 17. Desulfurization of **17** with W-2 Raney nickel afforded the methyl ketone **18**. The formation of the new methyl group in **18** was evident from its nmr spectrum. Catalytic hydrogenation of **18** in the presence of platinum afforded a two-spot mixture of the epimeric diols **19** which, without further purification, was converted into the corresponding dibenzoates, **20**, and pyrolyzed at 440°. The distillate on chromatography afforded methyl sandaracopimarate (**2**, 55% from **18**), which on ester cleavage using lithium iodide in collidine[24] gave (−)-sandaracopimaric acid (**1**) identical in all respects with an authentic sample of the natural acids.[25]

Experimental Section[26]

4α-Carbomethoxy-17β-acetoxy-5α-androst-1-en-3-one (4).—A solution of tritylsodium in ether (3%, 450 ml) was added to a solution of 17β-acetoxy-5α-androst-1-en-3-one[13] (9 g) in dry ether until the red color persisted. A stream of dry carbon dioxide was then bubbled into the mixture for 2 hr. The mixture was then stirred vigorously with ice water for 5 min, and the aqueous layer, after separation, was rapidly acidified with cold 10% sulfuric acid and immediately extracted with methylene chloride. The organic extract was treated with an excess of ethereal diazomethane solution for 10 min and then evaporated. The residue (six-spot mixture on tlc) was stirred with methanolic sulfuric acid (1%, 200 ml) overnight at room temperature, and the insoluble nonsteroidal solid was then removed by filtration. The filtrate was concentrated under reduced pressure, diluted with water, and extracted with methylene chloride. The extract was dried and evaporated under reduced pressure, and the residue was dissolved in pyridine (180 ml) containing acetic anhydride (40 ml). After being allowed to stand overnight at room temperature, the reaction mixture was diluted with ice water and after 15 min of stirring was extracted with ether. The extract was washed with cold 10% hydrochloric acid and water, dried, and evaporated. The resulting product (one major spot with trace contaminants) was applied as a plug on 600 g of Florisil. Elution with 20% ether–hexane afforded nonpolar materials and **3**. The material eluted with 30% ether–hexane was crystallized from ether–hexane to afford 3.17 g (30%) of **4** as colorless plates: mp 168–172°; $[\alpha]D$ −6.6°; λ_{max} 232 mμ (ε 10,400); λ_{max} 5.80, 6.00, and 8.10 μ; nmr δ 0.82 (3 H, s, 13-CH_3), 1.05 (3 H, s, 10-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 3.38 (1 H, d, 4β-**H**, J = 12.5 cps), 3.76 (3 H, s, 4-CO_2CH_3), 5.92 and 7.21 (1 H, d, 2-H and 1-**H**, J = 10 cps) ppm.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.11; H, 8.59.

4α-Carbomethoxy-17β-acetoxy-5α-androstan-3-one (6). A. From 4.—A solution of **4** (0.7 g) in methanol (15 ml) was added to a presaturated suspension of 10% palladized carbon (0.175 g) in methanol (15 ml) and the hydrogenation allowed to proceed under atmospheric conditions. After the uptake of hydrogen

(20) A. Afonso, *Can. J. Chem.*, **47**, 3693 (1969).

(21) J. Fajkos, *Collect. Czech. Chem. Commun.*, **20**, 312 (1955); **23**, 1559 (1958).

(22) R. O. Clinton, *et al.*, *J. Amer. Chem. Soc.*, **83**, 1478 (1961).

(23) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(24) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).

(25) The author thanks Dr. O. E. Edwards for a comparison sample of natural (−)-sandaracopimaric acid.

(26) Melting points were taken on a Reichert micro heating stage and are uncorrected. Infrared spectra were determined in Nujol mulls using a Perkin-Elmer Model 137 recording spectrophotometer. Ultraviolet spectra were determined on a Cary 14 spectrophotometer. Nmr spectra, in $CDCl_3$ using TMS as the internal standard, were determined on a Varian A-60A spectrometer. Specific rotations were measured on 0.3% solutions in dioxane at 26° unless otherwise specified. Silica gel GF (250 μ) plates from Analtech, Inc., were used for thin layer chromatography; 2.5% ethyl acetate in chloroform was used as the developing solvent and sulfuric acid as the spraying agent. Microanalyses and the physical measurements were performed by the Analytical Research Services, Schering Corp.

was complete (10 min), the catalyst was removed by filtration and the residue obtained by evaporation of the filtrate was crystallized from ethyl acetate–ether to afford 0.6 g of **6** as prisms: mp 159–161°; $[\alpha]D$ −2.8°; λ_{max} 5.72, 5.78, 5.84, 8.05 μ; nmr δ 0.82 (3 H, s, 13-CH_3), 1.06 (3 H, s, 10-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 3.27 (1 H, d, 4β-**H**, J = 12.5 cps), 3.76 (3 H, s, 4-CO_2CH_3) ppm.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.19; H, 8.97.

B. By Reductive Carbomethoxylation.—Clean lithium (2.0 g) was added in small pieces to liquid ammonia (400 ml). After all of the lithium had dissolved (*ca.* 1 hr), a solution of testosterone acetate in dry tetrahydrofuran (100 ml) was added to it during 5 min. The mixture was stirred for 45 min and then a few crystals of ferric chloride were added. After the blue color had discharged (15 min), the ammonia was evaporated off on a hot water bath. The last traces of ammonia were displaced by a stream of argon. The white residue was suspended in dry ether (500 ml) and Dry Ice (200 g) was added carefully to the suspension. Stirring was continued until the reaction mixture attained room temperature. It was then cooled, and cold water (200 ml) was added with efficient stirring immediately followed by cold 10% sulfuric acid until the aqueous layer was acidic. Stirring was continued for a short period until the material liberated in the aqueous layer was extracted into the ether layer. The stirring was stopped and excess ethereal diazomethane was added to the two-phase reaction. After 15 min excess diazomethane was decomposed with acetic acid and the ether layer was separated, dried, and evaporated. The residue was acetylated overnight at room temperature with a mixture of pyridine (200 ml) and acetic anhydride (45 ml). The mixture was worked up in the usual way and the crude product (tlc showed one major spot; however, polar materials at origin were present) was chromatographed over 800 g of Florisil. Elution with 10% ether–hexane afforded 0.6 g of nonpolar material. With 20% ether–hexane was eluted 2.2 g of a material having the same R_f as 17β-acetoxy-5α-androstan-3-one (**5**). Continued elution with the same solvent afforded a material which on crystallization from ethyl acetate–ether gave 6.6 g (24%) of **6**, mp 157–160°, identical (ir, tlc) with the material prepared as in **A**. Further elution afforded only polar materials.

4α-Methyl-4β-carbomethoxy-17β-acetoxy-5α-androst-1-en-3-one (11).—A solution of **4** (0.7 g) in dry benzene (15 ml), from which 5 ml of the solvent had been distilled, was cooled and stirred under argon with sodium hydride (45% in mineral oil, 0.11 g) at room temperature for 10 min and then heated under reflux for 2 hr. The mixture was cooled and stirred with methyl iodide (0.5 ml) for 2 hr at room temperature and then heated under reflux overnight. The reaction mixture, upon cooling, was washed with dilute hydrochloric acid and water, then dried, and evaporated. The residue (one spot by tlc), on crystallization from ethyl acetate, afforded 0.527 g (71%) of **11** as shiny flakes: mp 193–195°; $[\alpha]D$ +30.9°; λ_{max} 231 mμ (ϵ 9900); λ_{max} 5.79, 5.92, 8.05 μ; nmr δ 0.81 (3 H, s, 13-CH_3), 0.98 (3 H, s, 10-CH_3), 1.44 (3 H, s, 4-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 3.63 (3 **H**, s, 4-CO_2CH_3), 6.00 and 7.05 (1 H, d, 2-**H** and 1-**H**, J = 10 cps) ppm.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.21; H, 8.34.

Examination by tlc of the mother liquor from crystallization of **11** showed a homogeneous spot with the same R_f as **11**.

4α-Methyl-4β-carbomethoxy-17β-acetoxy-5α-androstan-3-one (8).—A solution of **11** (0.1 g) in methanol (5 ml) was added to a presaturated suspension of 10% palladized carbon (0.05 g) in methanol (5 ml). The hydrogenation was allowed to proceed under atmospheric conditions, and after the uptake of hydrogen had ceased (6 min) the catalyst was removed by filtration. The residue obtained by evaporating the filtrate was crystallized from ether to afford 0.085 g (84%) of **8** as colorless prisms: mp 200–201°; $[\alpha]D$ −7.3°; λ_{max} 5.75–5.82, 9.09, 9.23 μ; nmr δ 0.80 (3 **H**, s, 13-CH_3), 1.0 (3 H, s, 10-CH_3), 1.34 (3 H, s, 4-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 2.96 (1 H, sextet, 2β-**H**), J_{gem} = 14.5, $J_{2\beta\text{-H},1\alpha\text{-H}}$ = 14.5, $J_{2\beta\text{-H},1\beta\text{-H}}$ = 6 cps), 3.70 (3 H, s, 4-CO_2-CH_3) ppm.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.54; H, 8.99.

4β-Methyl-4α-carbomethoxy-17β-acetoxy-5α-androstan-3-one (7).—A solution of **6** (7.0 g) in dry benzene (150 ml), from which 50 ml of the solvent had been distilled, was alkylated with methyl iodide (5 ml) in the presence of sodium hydride (45% in mineral oil, 1.1 g) under conditions of reaction and work-up identical with those used for the preparation of **11**. The alkylation product on crystallization from ether afforded 3.18 g of **7** (one spot by tlc). The mother liquor (two spots by tlc) was evaporated to dryness and the residue was chromatographed over 200 g of Florisil. Elution with 10% ether–hexane afforded, after crystallization from ether, 0.428 g of **8**, mp 198–200°. The material was identical with **8** prepared by the hydrogenation of **11**.

Continued elution with the same solvent afforded, after crystallization from ether, an additional 1.46 g (total yield 4.64 g, 64%) of **7**. Recrystallization from ether–hexane afforded **7** as shiny plates: mp 166–168°; $[\alpha]D$ −24.1°; λ_{max} 5.75, 5.88, 9.23, 11.0 μ; nmr δ 0.80 (3 H, s, 13-CH_3), 1.06 (3 H, s, 10-CH_3), 1.37 (3 H, s, 4-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 3.71 (3 H, s, 4-CO_2CH_3) ppm.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.17; H, 8.99.

4β-Methyl-4α-carbomethoxy-5α-androstan-17β-ol (9).—A heterogeneous mixture consisting of **7** (4 g), toluene (40 ml), 15% hydrochloric acid (100 ml), and amalgamated zinc[27] (prepared from 90 g of zinc) was heated under reflux for 4 days (tlc indicated that the reaction was complete). During this period, concentrated hydrochloric acid (14 ml) was added to the mixture in 2-ml portions. The reaction mixture was cooled and extracted several times with ether, and the combined extracts were washed with water, dried, and evaporated. The residue (two spots by tlc due to partial hydrolysis of the 17-acetate) was dissolved in methanol (50 ml) and treated for 2.5 hr at room temperature with 10% sodium hydroxide (4 ml). The solution was concentrated under reduced pressure, acidified with dilute hydrochloric acid, diluted with ice water, and extracted with chloroform. The extract was dried and evaporated. The residue was taken up in 25 ml of methylene chloride and treated with an excess of an ethereal solution of diazomethane for 1 hr; the solution was then evaporated to dryness. The product on crystallization from methanol afforded 3.25 g (93%) of **9** as white plates: mp 173–178°; $[\alpha]D$ −6.7°; λ_{max} 2.89, 5.82, 7.61, 7.99, 8.46, 8.52, 9.73 μ; nmr δ 0.72 (3 H, s, 13-CH_3), 0.89 (3 H, s, 10-CH_3), 1.18 (3 H, s, 4-CH_3), 3.64 (3 H, s, 4-CO_2CH_3) ppm.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.90; H, 10.41.

4α-Methyl-4β-carbomethoxy-5α-androstan-17β-ol (10).—A mixture consisting of **8** (0.15 g), 15% hydrochloric acid (6 ml), toluene (1 ml), and amalgamated zinc[27] (from 6 g of zinc) was heated under reflux for 3 days. During this period concentrated hydrochloric acid (3.6 ml) was added in 0.6-ml portions. The reaction mixture was worked up as described in the preceding experiment, the hydrolysis step being carried out with 0.2 ml of 10% sodium hydroxide in 4 ml of methanol. Reesterification with diazomethane was not necessary. The product was crystallized from methanol to afford 0.085 g (66%) of **10** as needles: mp 180–184°; $[\alpha]D$ +37.1°; λ_{max} 2.85, 5.82, 7.51, 8.06, 8.52, 8.60, 8.92, 9.63 μ; nmr δ 0.70 (6 H, s, 13- and 10-CH_3), 1.16 (3 H, s, 4-CH_3), 3.65 (3 H, s, 4-CO_2CH_3) ppm.

Hydrolyses of Esters 9 and 10.—A solution of the ester (13 mg) in ethylene glycol (0.5 ml) containing 10% aqueous potassium hydroxide (0.1 ml) was heated in an oil bath at 150°. A micro cold finger was used instead of a condenser. Micro aliquots were taken at hourly intervals, acidified with dilute hydrochloric acid, and extracted with methylene chloride. The residue obtained from evaporation of the extract of each aliquot was analyzed by tlc. The 3-hr aliquots showed that ester **9** had hydrolyzed completely, while **10** was mainly unchanged.

The 3-hr aliquot of **9** was treated with ethereal diazomethane for 15 min and then examined by tlc. Complete regeneration of **9** was observed.

4β-Methyl-4α-carbomethoxy-5α-androstan-17-one (12).—A solution of **9** (3.1 g) in acetone (300 ml) was cooled to 10° and treated with Jones reagent (2.44 ml). The mixture was then stirred at room temperature for 10 min and filtered through Celite. The filtrate was concentrated under reduced pressure, diluted with ice water, and extracted with chloroform. The extract was dried and evaporated. The residue was chromatographed over 60 g of Florisil. The eluates with hexane were discarded. The desired product was eluted with 2% ether–hexane. Crystallization from hexane afforded 2.63 g (85%) of

(27) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p 199.

12 as needles: mp 140–142°; $[\alpha]_D$ +42.9°; λ_{max} 5.72, 5.76, 9.26 μ.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.44; H, 9.55.

4β-Methyl-4α-carbomethoxy-16α-bromo-5α-androstan-17-one (13).—A solution of **12** (2.6 g) in isopropenyl acetate (300 ml) containing *p*-toluenesulfonic acid (0.26 g) was distilled slowly (200 ml of distillate was collected in 10 hr) and then refluxed for 3 days. The dark brown reaction mixture was concentrated under reduced pressure, cooled, diluted with ethyl acetate, washed with 5% sodium bicarbonate solution and with water, and then dried and evaporated under reduced pressure. The residue (mainly one spot by tlc) was dissolved in carbon tetrachloride (100 ml). The solution was cooled in an ice bath and to it was added rapidly a cold solution of bromine (1.3 g) in carbon tetrachloride (25 ml). The solution was filtered to remove a tan solid that had coagulated out, and the pale yellow filtrate was evaporated to dryness. The residue (one spot by tlc) on crystallization from ether afforded 2.56 g (79%) of **13** as long needles: mp 220–224° dec; $[\alpha]_D$ +51.9°; λ_{max} 5.70, 5.79, 8.50 μ.

Anal. Calcd for $C_{22}H_{33}O_3Br$: C, 62.10; H, 7.81. Found: C, 62.23; H, 7.76.

4β-Methyl-4α-carbomethoxy-5α-androst-14-en-17-one (14).—A mixture of **13** (2.5 g), lithium bromide (2.5 g), and lithium carbonate (2.5 g) in dimethylformamide (25 ml) was heated at 180° under argon, with efficient stirring. After 4 hr, the reaction mixture was cooled, diluted with water, acidified with dilute sulfuric acid, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was dissolved in ether and treated with an excess of ethereal solution of diazomethane for 15 min at room temperature. The solution was then evaporated and the residue was chromatographed on 60 g of Florisil. The major product was eluted with 10% ether–hexane and crystallization from hexane afforded 0.65 g (32%) of **14** as prisms: mp 102–103°; $[\alpha]_D$ +104.6°; λ_{max} 5.70, 5.79, 8.01 μ; nmr δ 0.98 (3 H, s, 10-CH_3), 1.10 (3 H, s, 13-CH_3), 1.20 (3 H, s, 4-CH_3), 2.89 (2 H, m, 16-H_2), 5.52 (1 H, m, 15-H), 3.67 (3 H, s, 4-CO_2CH_3) ppm.

Ozonization of 14.—A stream of ozonized oxygen was bubbled through a gas dispersion tube into a solution of **14** (0.6 g) in ethyl acetate (10 ml) at −70° until the solution acquired a light blue color. The solution was allowed to stand for 10 min, after which excess ozone was displaced with a stream of argon and the solution as evaporated to dryness under reduced pressure. The residue on crystallization from ethyl acetate–ether afforded the ozonide **15** (0.65 g, 75%) as colorless plates: mp 179–185° dec; λ_{max} 5.79, 8.01, 9.01, 10.42 μ; nmr δ 0.91 (3 H, s, 10-CH_3), 1.18 (6 H, s, 13-CH_3 and 4-CH_3), 3.66 (3 H, s, 4-CO_2CH_3) ppm; ABX splitting for C_{15}–C_{16} protons: δ H_A 2.58, H_B 2.86 (2 H, octet, J_{AB} = 17.5, J_{AX} = 1.5, J_{BX} = 3.0 cps), H_X 5.96 (1 H, m, J_{AX+BX} = 5 cps) ppm.

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.18; H, 8.50.

Thioketal 17.—A solution of the ozonide **15** (0.48 g) in ethyl acetate (25 ml) was hydrogenated in the presence of 10% palladized carbon (0.3 g) which had been presaturated with hydrogen. The theoretical uptake of hydrogen (31 ml) was complete in 3 min. Removal of the catalyst by filtration and evaporation of the filtrate afforded **4β-methyl-4α-carbomethoxy-14,15-*seco*-15-hydroxy-5α-androst-15-en-17-one (16)** as a resinous solid, λ_{max} 259 mμ (ε 2760) → $\lambda_{max}^{MeOH-NaOH}$ 296 mμ (ε 12,600). Without further purification, **16** was dissolved in methanol (20 ml) containing ethylene *p*-toluenethiolsulfonate[28] (0.64 g) and potassium acetate (0.8 g). The mixture, under an argon blanket, was heated on the steam bath for 0.5 hr. The resulting pale yellow solution was then concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The residue obtained by evaporation of the organic extract was applied on a 20 × 20 × 0.1 cm silica gel plate which was then developed in 2% ethyl acetate–chloroform. The major band was extracted with 20% methanolic chloroform. Evaporation of the extract left a residue (one spot by tlc) which was crystallized from ether to afford 0.18 g (34%) of **17** as colorless plates: mp 158–161°; $[\alpha]_D$ −14.1°; λ_{max} 5.80, 5.92 μ; nmr δ 1.00 (3 H, s, 10-CH_3), 1.20 (3 H, s, 4-CH_3), 1.45 (3 H, s, 13-CH_3), 3.38 (4 H, m, -S-$(CH_2)_2$-S-), 3.67 (3 H, s, 4-CO_2CH_3), 5.10 (1 H, s, -CH(-S-)-S-) ppm.

Anal. Calcd for $C_{23}H_{34}O_4S_2$: C, 62.96; H, 7.81. Found: C, 62.90; H, 7.42.

Methyl Ketone 18.—A solution of **17** (0.15 g) in methanol (30 ml) was treated with W-2 Raney nickel (2 g) and the resulting suspension was stirred efficiently while being heated under reflux for 2 hr. The catalyst was then removed by filtration and the residue was crystallized from hexane to afford 0.115 g (97%) of **18** as colorless prisms: mp 122–123°; λ_{max} 5.80–5.96 μ; nmr δ 1.00 (3 H, s, 10-CH_3), 1.18 (3 H, s, 4-CH_3), 1.38 (3 H, s, 13-CH_3), 2.15 (3 H, s, -$COCH_3$), 3.65 (3 H, s, -CO_2CH_3) ppm.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.49; H, 9.18.

Methyl Sandaracopimarate (2).—A suspension of platinum oxide (0.1 g) in methanol (10 ml) was prereduced and to it was added **18** (0.08 g). The hydrogenation was allowed to proceed under atmospheric conditions overnight (12 ml of hydrogen uptake), and the solution was then filtered. The filtrate was evaporated to dryness and the residue of the diol mixture **19** (two spots by tlc) was dissolved in pyridine (1.4 ml) containing benzoyl chloride (0.12 ml). The mixture was heated (argon blanket) at 140° for 6 hr and then was cooled, diluted with water, and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, then with water, dried, and evaporated. The residue of the dibenzoate mixture **20** was pyrolyzed by distilling at 180° (0.05 mm) through a glass tube (45 cm long, 3-mm i.d.) filled with glass wool and maintained at 440°. The condensate from this pyrolysis was chromatographed on 2 g of Florisil. Elution with 5% ether–hexane afforded a chromatographically homogeneous oil (39 mg). The mobility on tlc and the infrared spectrum (film) of this oil was identical with that of authentic methyl (−)-sandaracopimarate (**2**).[29] The yield of **2** from **18** was 55%.

(−)-Sandaracopimaric Acid (1).—A mixture of synthetic methyl sandaracopimarate (**2**, 25 mg), obtained in the previous experiment, and anhydrous lithium iodide (0.1 g) in *s*-collidine (2.5 ml) was heated under reflux (argon blanket) for 8 hr. The reaction was then cooled, diluted with water, and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and water and then was dried and evaporated. The tan residue was applied on a column of 1 g of Florisil which was then eluted with ether. The residue obtained by evaporating the ether eluate was crystallized three times from methanol–water to afford colorless needles of (−)-sandaracopimaric acid (**1**, 12 mg, 50%): mp 165–168° (undepressed on admixture with authentic[29] **1**), $[\alpha]^{26}_D$ −19.8° (c 0.2, ethanol) (lit.[5a] $[\alpha]^{26}_D$ −20°). The mobility on thin layer chromatography and infrared spectrum of synthetic **1**, obtained as above, was identical with that of natural[25] **1**.

Registry No.—**1**, 23527-10-8; **2**, 1686-54-0; **4**, 24165-39-7; **6**, 23527-11-9; **7**, 23527-12-0; **8**, 23527-13-1; **9**, 23527-14-2; **10**, 23527-15-3; **11**, 24165-44-4; **12**, 23527-16-4; **13**, 23527-17-5; **14**, 23527-18-6; **15**, 24165-46-6; **16**, 24165-47-7; **17**, 24165-48-8; **18**, 23527-21-1.

Acknowledgment.—The author is indebted to Mr. M. Yudis, Mrs. H. Marigliano, and Dr. A. K. Ganguly for helpful discussions on nmr data.

(28) Kindly supplied by Dr. I. Pachter of Endo Laboratories.

(29) Obtained by treating authentic (−)-sandaracopimaric acid[25] with diazomethane.

Mechanistic Aspects of Oxazolone Reactions with α Nucleophiles

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The amino acid derived oxazolone, 2-phenyl-L-4-benzyloxazolone, was used in the continuation of our studies on the reactions of α nucleophiles (species containing two adjacent nucleophilic centers). Our experiments indicate that those α nucleophiles which show an enhanced nucleophilicity in relationship to their basicity are capable of a biphilic (electrophilic-nucleophilic) interaction with the carbonyl group of an oxazolone. Racemization may compete with ring opening for substituted hydrazines where biphilic pathways may be involved. Where this bifunctional attack is impossible, as, for example, in 1,1-dimethylhydrazine, no enhancement was found and a totally racemized product was isolated. We found that temperature, solvent, and concentration of reactants are important factors in ring opening *vs.* racemization reactions. For hydroxylamine-derived α nucleophiles, such as N-hydroxypiperidine and N-hydroxysuccinimide, which form active esters, racemization does not compete favorably with ring opening and products with high optical purity are obtained. These reactions can be understood as involving biphilic pathways. The N-hydroxypiperidine reaction may proceed through a zwitterionic attack, while the N-hydroxysuccinimide can be viewed as proceeding by a concerted pathway involving the carbonyl group of the N-hydroxy compound.

Goodman and McGahren[2a] reported that hydrazine hydrate reacts without racemization with the peptide oxazolone, 2-(1′-benzyloxycarbonylamino-1′-methyl)-ethyl-L-4-benzyloxazolone to give the ring-opened product, benzyloxycarbonylaminoisobutyryl-L-phenylalanine hydrazide. This is in contrast to the result found with amino acid esters and other nucleophiles in reaction with oxazolones,[2] where substantial racemization is generally found. Hydrazine belongs to a special class of compounds known as α nucleophiles, *i.e.*, compounds which possess two adjacent nucleophilic centers. Its extremely high nucleophilicity to basicity ratio prompted us to explore the nature of reactions of other α nucleophiles with the oxazolone moiety. We believe that insight in this area would lead to new and improved methods for the synthesis of peptides without racemization.

Synthesis of Various Hydrazides. A. From 2-Phenyl-L-4-benzyloxazolone.—The reaction of various hydrazine derivatives with 2-phenyl-L-4-benzyloxazolone was studied in a variety of solvents and at several temperatures. The effect of a large excess of nucleophilic reagent was also examined. The crude isolated material was compared by thin layer chromatography, infrared spectroscopy, and, in some cases, nuclear magnetic resonance spectroscopy to the product prepared *via* a nonracemizing route. The specific rotation of the crude material prepared from the oxazolone was measured and the value was compared with the specific rotation of the same compound synthesized *via* the nonracemizing route to determine the extent of racemization in each case.

In order to avoid dihydrazide formation,[2a] we added a large excess of hydrazine in anhydrous methanol in one portion to the oxazolone solution in anhydrous methanol (or tetrahydrofuran). An extremely rapid reaction was observed, even at 0°. A tlc taken 1 min after the combination of reactants showed the absence of any oxazolone.

t-Butyloxycarbonyl hydrazide (*t*-butyl carbazate) was allowed to react with the oxazolone in ether at 25°. Tlc indicated a slow reaction. To determine the extent of racemization we converted the isolated carbazate derivative into benzoyl phenylalanine hydrazide, a compound which was prepared in optically pure form by acid hydrolysis of the *t*-butyloxycarbonyl group.

Phenylhydrazines, *o*-methoxyphenylhydrazine, N,N-dimethylhydrazine, and *p*-nitrophenylhydrazine react cleanly with oxazolones to give the expected hydrazide derivatives, although, for the latter two compounds, reaction is slow and the yield of product isolated was low.

B. Synthesis of Optically Pure Hydrazides.—We obtained benzoyl-L-phenylalanine hydrazide as a chromatographically pure material by treatment of the corresponding methyl ester with hydrazine. By comparison with this material, we determined the extent of racemization in the reaction of 2-phenyl-L-4-benzyloxazolone with hydrazine, hydrazine acetate, and *t*-butyl carbazate (indirectly). In addition, this hydrazide was employed in the azide synthesis of the phenylhydrazide, N,N-dimethylhydrazide, and *o*-methoxyphenylhydrazide derivatives.

For *p*-nitrophenylhydrazine, the azide reaction failed to give the desired material in either the sodium nitrite or the modified butyl nitrite approach. The desired compound, benzoyl-L-phenylalanine *p*-nitrophenylhydrazide, was made by an indirect procedure. Benzyloxycarbonyl-L-phenylalanine was coupled with *p*-nitrophenylhydrazine using dicyclohexylcarbodiimide. Hydrogen bromide in glacial acetic acid removed the benzyloxycarbonyl group and the resulting hydrobromide salt was benzoylated in pyridine–dimethylformamide with benzoyl chloride.

The indirect procedure was also used to confirm the azide synthesis for the *o*-methoxyphenylhydrazine and N,N-dimethylhydrazine reactions.

Synthesis of Hydroxylamine Derivatives. A. From 2-Phenyl-L-4-benzyloxazolone.—The parent compound, hydroxylamine, reacts with oxazolone under our reaction conditions to give two initial products. On continued reaction with an excess of hydroxylamine, one material disappears and the second increases in intensity. Apparently both O and N acylation occur. O-acyl derivatives are active esters and on further reaction with hydroxylamine are converted into the stable hydroxamic acids.[3] Spontaneous rearrangement of O-acyl to N-acyl derivatives has also been reported.[4]

(1) Submitted in partial fulfillment of the requirements for the Ph.D. Degree in Chemistry at the Polytechnic Institute of Brooklyn.

(2) (a) M. Goodman and W. J. McGahren, *Tetrahedron*, **23**, 2031 (1967); (b) M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, **86**, 2918 (1964).

(3) W. P. Jencks, *ibid.*, **80**, 4581, 4585 (1958).

(4) S. Bittner, Y. Knobler, and M. Frankel, *Tetrahedron Lett.*, 95 (1965).

N,N-Diethylhydroxylamine, N-hydroxypiperidine, and N-hydroxysuccinimide react rapidly to give product, while N,O-dimethylhydroxylamine reacts considerably more slowly under similar reaction conditions.

B. Attempted Synthesis of Optically Pure Hydroxylamine Derivatives.—The azide reaction with hydroxylamine gave a low yield of the stable hydroxamic acid. N,N-Diethylhydroxylamine failed to give the desired product by this method. For this reason, and also because little is known about oxygen attack on the carbonyl function of the azide, this route was not pursued for N-hydroxypiperidine or N-hydroxysuccinimide. The indirect procedure was also unsuccessful for the preparation of the optically pure N,N-diethylhydroxylamine ester of benzoyl-L-phenylalanine. This method involves benzoylation of a free amino acid activated ester in the final step. This species can form oligomers, small cyclic peptides, or the diketopiperazine. In addition, the active ester might racemize under these conditions, which would defeat the purpose of preparing the optically pure derivative. These considerations also apply to the active esters of N-hydroxypiperidine and N-hydroxysuccinimide. Therefore, we employed another approach to determine the extent of racemization for these active esters. They were converted with hydrazine (under conditions which do not involve racemization) into benzoylphenylalanine hydrazide, which was examined to ascertain its optical purity.

Finally, we employed the indirect procedure for the preparation of the N,O-dimethylhydroxylamine derivative.

Results and Discussion

It has been possible to correlate reactivities of various nucleophiles by suitable examination of such parameters as polarizability and basicity.[5-8] One class of compounds does not appear to follow these correlations in its reaction with certain electrophilic centers, in particular with activated carbonyl compounds. These nucleophiles are more reactive than would be predicted on the basis of polarizability and basic strength.[9-11] Their common structural feature is the presence of an unshared pair of electrons on the atom adjacent to the nucleophilic atom. Edwards and Pearson[12] noted that these nucleophiles exhibit an enhanced reactivity, which they termed the α effect.

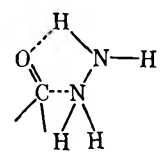
Hydrazine represents an example of this special group of vicinally bifunctional nucleophiles. As mentioned previously, Goodman and McGahren demonstrated that an excess of hydrazine hydrate reacts with the peptide oxazolone from benzyloxycarbonylaminoisobutyryl-L-phenylalanine, yielding optically pure hydrazide.[2a] Siemion and Morawiec[13] reported similar results with the oxazolone from acetyl-L-leucine. In contrast, Siemion and Dzugaj[14] reported that the ammonolysis of the oxazolone from acetyl-L-leucine gives completely racemic product.

Hydroxylamine and its derivatives are also α nucleophiles and have been found to have enhanced nucleophilicity.[9-11] Diethylhydroxylamine,[4] N-hydroxypiperidine,[15-17] N-hydroxyphthalimide,[18,19] N-hydroxysuccinimide,[20-23] and benzohydroxamic acid[24] have all been used in recent years as racemization-resistant activating agents in peptide coupling reactions.

Bruice and coworkers[11] outlined various proposed explanations for the α effect. They can be summarized briefly as follows: (A) stabilization of the transition state owing to overlap of the orbitals of the lone-pair electrons in the α position; (B) diminished solvation, *e.g.*, of HOO^- compared with OH^-; (C) ground-state destabilization resulting from nonbonding electron-pair repulsions; (D) intramolecular general base catalysis; (E) simultaneous push–pull mechanisms resulting from the "biphilic" nature of the reagent.

Most of the available evidence supports biphilic pathways for the α effect: (A) α nucleophiles which cannot participate in push–pull transition states are found to have normal reactivity;[9-11] (B) the α effect is inoperative in amine general base catalyzed ionization of nitroethane;[25] (C) the α effect is inoperative for displacements on sp^3 carbon (CH_3I);[26] (D) phenylhydroxylamine has a higher rate, lower E_a, and a high negative $\Delta S^{\pm}$ in relation to other nucleophiles in its attack on acetyl peroxide.[27] The high negative $\Delta S^{\pm}$ is indicative of a cyclic transition state.

This bifunctional pathway can be illustrated for the reaction of hydrazine with an activated carbonyl compound (ester, acid halide, acylisourea, anhydride, etc.) as follows.



In the transition state, hydrazine acts in a dual capacity by both supplying electron density for nucleophilic attack at the carbonyl carbon and withdrawing electron density from the electrophilic site by hydrogen bonding to the carbonyl oxygen.

Our studies on 2-phenyl-L-4-benzyloxazolone support these conclusions (Tables I and II). Oxazolones can be viewed in their reactions as members of the general

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(7) R. F. Hudson, *Chimica*, **16**, 173 (1962).
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(14) I. Z. Siemion and A. Dzugaj, *Rocz. Chem.*, **40**, 1699 (1966).
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(16) F. Weygand and W. König, *Z. Naturforsch.*, **20b**, 710 (1965).
(17) J. H. Jones, B. Liberek, and G. T. Young, *Proc. 8th Eur. Peptide Symp.* (Noordwijk), 15 (1966).
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(20) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **85**, 3039 (1963); **86**, 1839 (1964).
(21) E. Wünsch and F. Drees, *Chem. Ber.*, **99**, 110 (1966).
(22) F. Weygand, D. Hoffman, and E. Wünsch, *Z. Naturforsch.*, **21b**, 426 (1966).
(23) J. E. Zimmerman and G. W. Anderson, *J. Amer. Chem. Soc.*, **89**, 7151 (1967).
(24) E. Taschner, B. Rzeszotarska, and L. Lubiewska, *Chem. Ind.* (London), 402 (1967).
(25) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2327 (1967).
(26) M. J. Gregory and T. C. Bruice, *ibid.*, **89**, 4400 (1967).
(27) K. M. Ibne-Rasa and J. O. Edwards, *ibid.*, **84**, 763 (1962).

TABLE I

REACTIONS OF 2-PHENYL-L-4-BENZYLOXAZOLONE WITH HYDRAZINE AND ITS DERIVATIVES

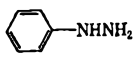
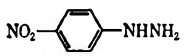
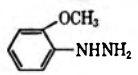
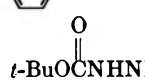
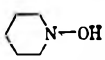
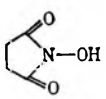
Nucleophile	Solvent	Temp, °C	Racemization, %	Nucleophile/ oxazolone
NH_2NH_2	THF–MeOH (1:1)	0	0	Large excess
	THF–MeOH (1:1)	25	14	Large excess
	THF–MeOH (1:1)	44	32	Large excess
$NH_2NH_2 \cdot HOAc$	THF	0	33	2.6:1
	THF	25	35	2.6:1
	Et_2O	0	35	1.1:1
	Et_2O	0	75	5:1
	Et_2O	25	70	1.1:1
	THF	0	100	5:1
	$CHCl_3$	0	33	1.1:1
	$CHCl_3$	25	59	1.1:1
	THF	25	100	1.1:1
	Et_2O	25	40	1.1:1
	Et_2O	25	75	1.2:1
$(CH_3)_2NNH_2$	Et_2O	25	100	1.1:1
	$CHCl_3$	0	100	1.1:1
	$CHCl_3$	25	100	1.1:1
	$CHCl_3$	25	100	8:1

TABLE II

REACTIONS OF 2-PHENYL-L-4-BENZYLOXAZOLONE WITH HYDROXYLAMINE AND ITS DERIVATIVES

Nucleophile	Solvent	Temp, °C	Racemization, %	Nucleophile/ oxazolone
NH_2OH	MeOH	25	0	2.5:1
	Et_2O	0	<5	1.1:1
	Et_2O	25	<10	1.1:1
	THF	25	<10	1.1:1
	THF	0	0	1.1:1
	THF	25	0	1.1:1
	THF	0	0	4:1
CH_3NHOCH_3	Et_2O	25	55	1.1:1
$(CH_3CH_2)_2NOH$	Et_2O	0	42	1.1:1
	Et_2O	25	56	1.1:1
	THF	0	42	1.1:1

class of activated carbonyl compounds. Those α nucleophiles which can participate in biphilic attack were found to react more rapidly and to give products with a considerably higher degree of optical purity than α nucleophiles which cannot participate in biphilic attack.

A large excess of hydrazine reacts instantaneously with oxazolone, even at 0°, and at this temperature no racemization is found. As the temperature is raised, racemization begins to compete more favorably. This may be a reflection of the highly ordered cyclic transition state necessary for bifunctional attack leading to ring-opened product.

In the series hydrazine, phenylhydrazine, and *p*-nitrophenylhydrazine, the increase in electron-withdrawing effect on the substituted nitrogen atom leads to a decrease in the ring-opening rate and more racemization. Apparently, the weakened nucleophilicity of the primary nitrogen atom is more important than the increased ability for electrophilic attack by the hydrogen atom on the substituted nitrogen. This also serves to explain the high degree of racemization found with *t*-butyl carbazate. A separate experiment was carried out with this nucleophile in which a first crop of product was isolated after 2 hr and a second crop at the completion of reaction. The first crop exhibited a considerably higher optical purity. This is consistent with two separate mechanisms for racemization and ring opening. The reagent, in this case *t*-butyl carbazate, may react with the oxazolone to form the ring-opened hydrazide. It may also act as a base, racemizing the oxazolone by removing the acidic proton from the asymmetric carbon atom. This racemized material may subsequently be ring opened to form product. For this reason, the product formed early in the reaction will have the highest specific rotation.

For phenylhydrazine, we can see that in ether at 0° a fivefold excess of the nucleophile causes substantially more racemization than a 10% excess causes. This is expected because of the increased polarity of the solution.

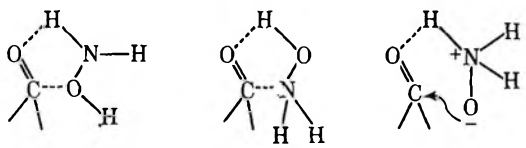
N,N-Dimethylhydrazine is a slightly weaker base than hydrazine in aqueous media.[28] Nevertheless, on reaction with oxazolone under a variety of conditions, complete racemization is found in a relatively slow reaction. No biphilic mechanism leading to product can be viewed for this nucleophile. Attack by the primary amine function does not allow for hydrogen bonding. Hydrogen bonding is possible for attack by the dimethyl nitrogen atom. This cannot lead to product, however, because the dimethyl nitrogen atom has no proton to expel and cannot eliminate the positive charge acquired during nucleophilic attack. Steric hindrance may also play a role in this reaction.

Hydroxylamine and its derivatives are considerably less basic than the corresponding hydrazine compounds;

(28) R. L. Hinman, *J. Org. Chem.*, **23**, 1587 (1958).

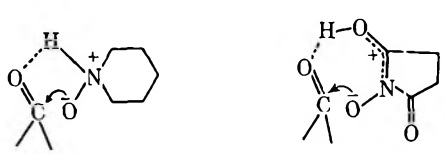
nevertheless, reactions of bifunctional reagents hydroxylamine, N-hydroxypiperidine, N-hydroxysuccinimide, and N,N-diethylhydroxylamine with oxazolone are very fast and the optical purity of the compounds obtained in the first three cases is high (90–100%).

Reaction of the parent compound, hydroxylamine, involves competition between oxygen and nitrogen attack on the carbonyl function. Either reaction may involve bifunctional attack by the neutral hydroxylamine molecule (transition state **1a,b**). In addition, oxygen anion attack by the zwitterionic form of the molecule may also be involved in a push–pull mechanism (transition state **1c**). This latter possibility can account for the initial formation of considerable O-acyl derivative.



1a **1b** **1c**

In the reaction of N-hydroxypiperidine, no biphilic mechanism is possible for the neutral species. However, in the zwitterionic form, reaction may proceed *via* attack by the oxygen anion and simultaneous hydrogen bonding (transition state **2a**). The greater degree of racemization found for N,N-diethylhydroxylamine (42–56%) compared with N-hydroxypiperidine (5–10%) can be explained by steric considerations which would retard the ring-opening reaction. Racemization by proton abstraction should be much less sterically dependent. The alkyl substituents on the N atom of N-hydroxypiperidine are restrained by the ring. These restrictions on rotation do not apply to N,N-diethylhydroxylamine. Consequently, the approach of N,N-diethylhydroxylamine to the oxazolone system should be more sterically hindered and causes more racemization. For N-hydroxysuccinimide, a simple zwitterion (analogous to **2a**) is not likely because of the electronegative effect of the two carbonyl functions adjacent to the nitrogen atom. However, in the delocalized zwitterionic structure illustrated (transition state **2b**), the dispersal of positive charge through three atoms makes possible an enhanced rate of reaction *via* a nucleophilic–electrophilic mechanism. This zwitterionic structure need only be present in extremely low concentration in equilibrium with the more stable unchanged form. It should be noted that hydroxamic acids normally react in aqueous solution as anions. Perhaps the anionic form is the reacting species of N-hydroxysuccinimide in organic media. N,O-Dimethylhydroxylamine can neither participate in a biphilic attack in the transition state nor form a zwitterionic intermediate. Consequently, it ring opens oxazolone considerably more slowly and the product derived is substantially racemized.



2a **2b**

The results of Siemion[29] are consistent with our biphilic interpretation of α-nucleophilic effects involving hydrogen bonding to the carbonyl oxygen of the oxazolone ring. However, he proposed an alternate biphilic mechanism based on the influence of the weakly basic nitrogen atom in the oxazolone ring. Siemion suggests that as the oxazolone ring opens, the basicity of the ring nitrogen is strongly enhanced, leading to racemization by abstraction of hydrogen from the adjacent carbon atom. According to this explanation, attack by hydrazine involves hydrogen bonding to the nitrogen atom of the ring and accounts for the lack of racemization.

We believe that the mechanism proposed by Siemion is incorrect because oxazolone racemization is extremely facile during peptide coupling. The strong bases present abstract the proton from the asymmetric carbon. The weakly basic nitrogen of the oxazolone ring cannot compete. Ring opening and racemization can thus be seen as two distinct and coexisting processes.

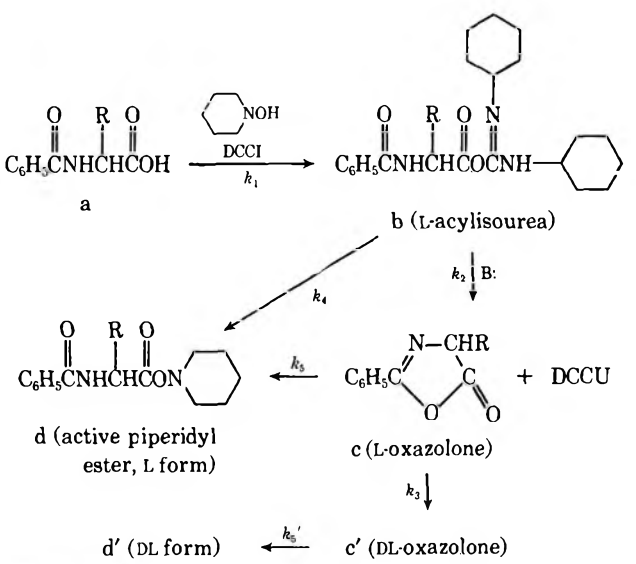
(A) The wide variance in k_{ro}/k_{rac} found for different amino acid esters in reaction with the peptide oxazolone 2-(1′-benzyloxycarbonylamino-1′-methyl)-ethyl-L-4-benzyloxazolone[2a] implies two separate processes for ring opening and racemization. It follows from Siemion's proposal that each of these reactions should have similar k_{ro}/k_{rac} ratios.

(B) For highly hindered nucleophiles such as methyl aminoisobutyrate, $k_{rac} \gg k_{ro}$, and in general $k_{rac} \geq k_{ro}$.[2a] Siemion's proposal leads to a prediction that $k_{rac} \leq k_{ro}$ in all cases.

(C) Tertiary amines,[2a] and even the much less basic dicyclohexylcarbodiimide, lead to rapid racemization of the oxazolone, even though ring opening is impossible for these compounds.

(D) The experiment on partial isolation of product with *t*-butyl carbazate, described in the previous section, is consistent only with separate processes for racemization and ring opening.

It appears that biphilic attack involving hydroxylamine-derived activating groups makes possible the preparation of the active ester in a higher degree of optical purity than would otherwise be found. For example, we can illustrate the preparation of an N-



(29) I. Z. Siemion, *Rocz. Chem.*, **42**, 237 (1968).

hydroxypiperidine active ester from a benzoyl amino acid using dicyclohexylcarbodiimide. (An analogous argument could be used employing the mixed anhydride route.)

Analysis of the reaction after formation of the initial species (b) leads us to the following predictions.

(A) The k_4/k_2 value will be substantially higher for N-hydroxypiperidine, where a biphilic mechanism is operative, than for *p*-nitrophenol, where it is not. Little oxazolone (c) formation is expected in the first case, whereas substantial oxazolone may be formed in the second.

(B) Even if L-oxazolone (c) were to form extensively, biphilic attack of N-hydroxypiperidine would lead to optically active d. Thus k_5/k_3 will be much higher than for *p*-nitrophenol, where no biphilic route is possible.

It cannot be stated at this time which of these factors is most important, but the net effect is clear. Intermediates which are obtained *via* biphilic reactions will have a high degree of optical purity.

As part of a comprehensive study on the chemistry of carbodiimides,[30-32] DeTar and his associates studied the reactions of peptide acids with carbodiimides.[30] They found that the rate of reaction between benzoylphenylalanine and dicyclohexylcarbodiimide is the same with or without *p*-nitrophenol present. Oxazolone is the first identifiable intermediate, confirming earlier results.[33] Under the reaction conditions, the rate of reaction to form oxazolone from benzoylphenylalanine is 1000 times faster than the reaction of oxazolone with *p*-nitrophenol. As we noted earlier, Goodman and Levine[2b] found that the reaction of isolated oxazolone from benzoyl-L-phenylalanine and *p*-nitrophenol is reversible, and racemization proceeds much more rapidly than ring opening for attack by *p*-nitrophenylate anion. There have been several reports of racemization during the preparation of *p*-nitrophenyl esters of acylated derivatives from both the dicyclohexylcarbodiimide[2,30,34,35] and tris-*p*-nitrophenyl phosphite methods.[36]

Conclusions

Our research has centered on the chemistry of oxazolones, particularly in their relationship to racemization and peptide coupling reactions. Stable, optically active oxazolones offer the chemist a unique system for studying the nucleophilicity and basicity of various compounds in organic solvents. Examining this system with α nucleophiles, we explored the special nature of these reagents, which allows for a stronger nucleophilic effect than would otherwise be expected. Participapation in a concerted mechanism involving nucleophilic–electrophilic attack can account for the enhanced rate of ring opening. The implication for the formation of peptide-active esters derived from α nucleophiles was discussed.

It is recognized that our studies represent the most unfavorable situation possible in peptide coupling, *i.e.*, where all the acyl peptide is present as oxazolone. For this reason, the very low degree of racemization found for hydroxylamine compounds in cases where biphilic attack is possible is quite significant.

Experimental Section

All melting points are uncorrected. They were obtained on a Kofler hot stage melting point apparatus. Analyses were carried out by Alfred Bernhardt Mikroanalytisches Laboratorium, Max Planck Institut, Mülheim, West Germany. Solvents used in reactions involving oxazolone were anhydrous. Gelman type SG silica chromatograms were used for tlc with iodine as the developing agent. Chloroform and chloroform–hexane mixtures were used for chromatographic separation.

N-Benzoyl-L-phenylalanine.—This compound was prepared in 59% yield by the procedure of Greenstein and Winitz,[37] mp 142–143°, $[\alpha]^{25}D$ +38.50° (c 1.5, dioxane) [lit.[2b] mp 142–143°, $[\alpha]^{25}D$ +38.74° (c 1.6, dioxane)].

2-Phenyl-L-4-benzyloxazolone. A. Using Dicyclohexylcarbodiimide.—A solution of dicyclohexylcarbodiimide (1.65 g, 8.0 mmole) in 5 ml of anhydrous ether was added to benzoyl-L-phenylalanine (2.15 g, 8.0 mmol) in 30 ml of anhydrous ether at 0.5°. Precipitation of dicyclohexylurea began almost immediately. After 15 min the solution was filtered and the ether was removed at room temperature under reduced pressure to give a solid material. Fresh ether (20 ml) was added, the solution was filtered again, and the solvent was removed. The solid product was recrystallized from *ca.* 1:1 ether–petroleum ether (bp 30–60°). *Ca.* 30 ml of total volume was sufficient. No cloud point was noticed on addition of petroleum ether, but 1.50 g (75%) of crystalline material formed on cooling for 1–2 hr in the refrigerator, mp 86.0–87.5°, $[\alpha]^{25}D$ −67.0° (c 2, dioxane).

A second recrystallization was sufficient to raise the rotation to −71.0° and the melting point to 88–89°, but the overall yield was reduced to 1 g (50%). After drying over P_2O_5 under reduced pressure, this compound was stored in the refrigerator. No decomposition or racemization was found under these conditions after several months [lit.[2b] mp 86.6–87.2°, $[\alpha]^{25}D$ −71.20° (c 0.5, dioxane)]. This is the preferred method of preparation.

B. Using Acetic Anhydride.—A solution of 1.0 g of benzoyl-L-phenylalanine in 5.5 ml of dioxane and 5.5 ml of acetic anhydride was prepared, and the change in rotation was followed in the polarimeter (Table III).

TABLE III

Time, min	Rotation, deg	Time, min	Rotation, deg
2.33	+1.534	57.83	−4.510
3.87	+1.249	60.00	−4.570
5.43	+0.967	64.83	−4.680
8.00	+0.500	66.50	−4.730
10.93	+0.041	68.00	−4.744
15.00	−0.600	70.00	−4.760
22.93	−1.659	75.08	−4.790
31.00	−2.534	77.50	−4.785
36.00	−3.018	84.50	−4.717
41.17	−3.467	94.00	−4.620
43.25	−3.607	99.50	−4.513
52.75	−4.317	107.33	−4.393

After 70 min, the solvent was removed under reduced pressure at room temperature. Dry toluene (15 ml) was added twice to the remaining crude material and the solution was evaporated to dryness each time. Recrystallization was effected from ether–hexane to give a yield of 40%, mp 86–87°, $[\alpha]^{25}D$ −68.0° (c 2, dioxane).

Benzoyl-L-phenylalanine Methyl Ester.—Diazomethane prepared from 10.0 g of 80% N-nitroso-N-methylurea (20% acetic acid) was added to benzoyl-L-phenylalanine (7.50 g, 26.5 mmol) in 35 ml of methylene chloride at 0°. The yellow ether–methylene

(30) D. F. DeTar, R. Silverstein, and F. F. Rogers, Jr., *J. Amer. Chem. Soc.*, **88**, 1024 (1966).
(31) D. F. DeTar and R. Silverstein, *ibid.*, **88**, 1013 (1966).
(32) D. F. DeTar and R. Silverstein, *ibid.*, **88**, 1020 (1966).
(33) M. M. Botvinik, S. N. Kara-Murza, S. M. Avaeva, and V. Ya. Nikitin, *Dokl. Akad. Nauk. SSSR*, 88 (1964).
(34) J. Kovacs, unpublished results.
(35) W. D. Cash, *J. Org. Chem.*, **27**, 3329 (1962).
(36) M. Goodman and K. C. Stueben, *ibid.*, **27**, 3409 (1962).
(37) J. P. Greenstein and M. W. Winitz, "Chemistry of the Amino Acids," John Wiley & Sons, Inc., New York, N. Y., 1961, p 1267.

chloride solution was evaporated to dryness after 2 hr in a stream of nitrogen. Fresh ether (50 ml) was added and the process was repeated. The white solid was taken up in ether, extracted with 10% K_2CO_3, saturated KCl, 5% HCl, and saturated KCl again, and then dried. After filtration, evaporation of solvent, and trituration with hexane, 6.3 g of crude material was obtained which gave a first crop of 5.0 g of pure product on recrystallization from ether–hexane, mp 82–83°, $[\alpha]^{25}D$ +24.0° (*c* 1, dioxane) [lit.[2] mp 83.6–84.6°, $[\alpha]^{25}D$ +24.2° (*c* 1, dioxane)]. A second crop of 550 mg of pure material was also recovered, total yield 67%.

Benzoyl-L-phenylalanine Hydrazide. A. From Benzoyl-L-phenylalanine Methyl Ester.—To benzoyl-L-phenylalanine methyl ester (5.00 g, 17.6 mmol) in 20 ml of methanol at the boiling point, 6 ml of anhydrous hydrazine (97%, large excess) was added and the solution was allowed to stand for 24 hr, being cooled in the ice box before filtration. Crystallization was observed on cooling to room temperature; 4.40 g of crude product was obtained. Recrystallization from methanol yielded 3.55 g (71%) of material, mp 193–198°, $[\alpha]^{25}D$ −45.8° (*c* 1.5, dimethylformamide).

Anal. Calcd for $C_{16}H_{17}O_2N_3$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.85; H, 6.04; N, 15.11.

B. From 2-Phenyl-L-4-benzyloxazolone. Procedure 1.—Oxazolone (320 mg, 1.27 mmol) in 10 ml of anhydrous methanol was added to 1 ml of anhydrous hydrazine (97%) in 10 ml of anhydrous methanol at 0°. A crystalline precipitate was noted instantaneously. After 15 min the solvent was removed at room temperature over sulfuric acid under reduced pressure to remove traces of hydrazine. The solid was washed with ether and filtered to give 300 mg (84%) of crude product, mp 190–197°, $[\alpha]^{25}D$ −45.3° (*c* 1, dimethylformamide). Recrystallization from methanol gave chromatographically pure product, mp 192–196°, $[\alpha]^{25}D$ −45.6° (*c* 1, dimethylformamide).

Anal. Calcd for $C_{16}H_{17}O_2N_3$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.86; H, 5.99; N, 14.95.

This experiment was repeated using tetrahydrofuran as a solvent for the oxazolone and with an inverse order of addition to the above. The results obtained were identical with those reported. In addition, hydrazine hydrate (85%) was used in both methanol and the mixed methanol–tetrahydrofuran solvent system. In all cases, at 0°, no racemization was found.

Procedure 2.—Hydrazine hydrate (3 ml, large excess) in 5 ml of methanol at 25° was added to oxazolone (251 mg, 1 mmol) in 5 ml of tetrahydrofuran. Work-up as described above gave product in 90% yield, $[\alpha]^{25}D$ −39.2° (*c* 1, dimethylformamide).

A similar run with anhydrous hydrazine (97%) in fivefold excess afforded a product, $[\alpha]^{25}D$ −39.5° (*c* 1, dimethylformamide).

Procedure 3.—Anhydrous hydrazine (250 mg, 7.8 mmol) in 5 ml of anhydrous methanol was added to 2-phenyl-L-4-benzyloxazolone (251 mg, 1 mmol) in 5 ml of tetrahydrofuran at 44°. Work-up gave product in 87% yield, $[\alpha]^{25}D$ −30.7° (*c* 1, dimethylformamide).

C. From Indirect Route Using *t*-Butyloxycarbonyl Hydrazide. Procedure 1. Benzoylphenylalanine *t*-Butyloxycarbonyl Hydrazide.—*t*-Butyloxycarbonyl hydrazide (380 mg, 2.9 mmol, prepared by the method of Carpino[38]) in 5 ml of ether was added to 2-phenyl-L-4-benzyloxazolone (600 mg, 2.4 mmol) in 10 ml of anhydrous ether at room temperature. Thin layer chromatography indicated a slow reaction. After 5 hr, substantial oxazolone remained. Precipitation of product began after 1 hr.

In the first run, 260 mg of material was filtered off after 2 hr, and the material gave one spot with tlc after washing with cold ether. A second crop of 500 mg with an identical thin layer chromatogram and infrared spectrum was obtained on completion of reaction: fraction 1, 260 mg, mp 165–167°, $[\alpha]^{25}D$ −63.7° (*c* 2, dimethylformamide); fraction 2, 500 mg, mp 100–105°, $[\alpha]^{25}D$ −22.9° (*c* 2, dimethylformamide). Obviously, as time passes, the material formed is more highly racemized.

In the second run, the reaction was allowed to run overnight to completion at room temperature. Crude product (800 mg, 87.3%) was obtained on filtration and washing with cold ether. No additional product could be seen in the tlc of the solution. The product gave one spot with tlc, mp 148–150°, $[\alpha]^{25}D$ −31.8° (*c* 2, dimethylformamide). This material was used in the hydrolysis step.

(38) (a) L. A. Carpino, *J. Org. Chem.*, **28**, 1909 (1963); (b) *J. Amer. Chem. Soc.*, **82**, 2725 (1960).

Procedure 2. Benzoylphenylalanine Hydrazide.—Benzoyl phenylalanine *t*-butyloxycarbonyl hydrazide (500 mg, 1.30 mmol) was added to 7 ml of a dry, saturated solution of hydrochloric acid in tetrahydofuran at 0°. Evolution of carbon dioxide was noticed. The solution was allowed to warm to room temperature, and after 2 hr the cloudy mixture was precipitated by adding it to 200 ml of ether. After cooling in the refrigerator for 1 hr, 270 mg of crude product (65%) was obtained after filtration and washing with ether. Neutralization was accomplished by adding a concentrated solution of $NaHCO_3$ to this material. After 1 hr, the product was removed by filtration, washed with water, and dried under reduced pressure over P_2O_5. The hydrazide was obtained, mp 180–188°, $[\alpha]^{25}D$ −12.7° (*c* 1, dimethylformamide).

Anal. Calcd for $C_{16}H_{17}O_2N_3$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.78; H, 5.99; N, 15.00.

D. From 2-Phenyl-L-4-benzyloxazolone and Hydrazine Acetate.—A solution of acetic acid (660 mg, 1.0 mmol) in 10 ml of tetrahydrofuran was added to anhydrous hydrazine (320 mg, 1.0 mmol) in 5 ml of tetrahydrofuran. The immediate formation of an insoluble material was noted. This was filtered off, washed with tetrahydrofuran, dried *in vacuo* over P_2O_5, and used without further characterization.

The hydrazine acetate salt (240 mg, 2.6 mmol), suspended in 10 ml of tetrahydrofuran, was added to L-oxazolone (251 mg, 1.0 mmol) in 5 ml of tetrahydrofuran at room temperature and stirring was continued for 4 hr. The solvent was evaporated at room temperature with a stream of nitrogen, water was added, and the product was filtered and dried *in vacuo* over P_2O_5 and concentrated H_2SO_4. Product (210 mg, 74%) was obtained, identifiable from its thin layer chromatogram and infrared spectrum, $[\alpha]^{25}D$ −39.5° (*c* 1.5, dimethylformamide).

The same reaction was repeated at 0° for 6 hr. Identical work-up afforded 215 mg (76%) of product, $[\alpha]^{25}D$ −29.6° (*c* 1.5, dimethylformamide).

In both cases, thin layer chromatography showed only one material, while the infrared spectra indicated minor impurities.

Benzoylphenylalanine Phenylhydrazide. A. Azide Route.—To benzoyl-L-phenylalanine hydrazide (566 mg, 2 mmol) in 0.1 *N* hydrochloric acid (40 ml, 4 mmol), 10 ml of glacial acetic acid was added to bring about solution. The solution was cooled to −5°, and a solution of $NaNO_2$ (280 mg, 4 mmol) in 15 ml of H_2O at 0° was added dropwise over 3 min. The azide formed immediately as an insoluble, white solid. After 10 min, the azide was extracted into 40 ml of a 1:1 mixture of methylene chloride–ether, and this solution was extracted with ice-cold solutions of saturated KCl, 5% $NaHCO_3$ (until basic), and once again with KCl and dried ($MgSO_4$) at −15°. The dry organic solution was filtered and added in one portion to phenylhydrazine (0.3 ml, 0.329 g, 3 mmol) in 10 ml of ether at 0°. The solution was stirred overnight and allowed to warm to room temperature after *ca.* 8 hr. After 50 ml of petroleum ether had been added, 400 mg (55.7%) of crude product was isolated on cooling. Recrystallization from methanol gave 287 mg (40%) of product, mp 197–208°, $[\alpha]^{25}D$ −69.9° (*c* 1.5, dimethylformamide).

Anal. Calcd for $C_{22}H_{21}O_3N_3$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.30; H, 5.94; N, 11.99.

B. From Oxazolone.—Experiment B was run as follows. Phenylhydrazine (120 mg, 1.1 mmol) in 5 ml of ether at room temperature was added to 2-phenyl-L-4-benzyloxazolone (251 mg, 1.0 mmol) in 10 ml of ether. Precipitation of product began within 5 min. After 2.5 hr at room temperature, the solvent was removed and petroleum ether was added. Product (350 mg, 92.0%) was obtained on filtration and washing with cold ether–petroleum ether, $[\alpha]^{25}D$ −21.1° (*c* 1, dimethylformamide). One spot was obtained with tlc, which corresponded to that from the azide reaction. Recrystallization from ethanol afforded an analytical sample, mp 199–207°.

Anal. Calcd for $C_{22}H_{21}O_2N_3$: C, 73.35; H, 5.88; N, 11.79. Found: C, 73.52; H, 5.89; N, 11.69.

This reaction was repeated under several conditions (Table IV).

C. From Succinimide Active Ester.—Benzoyl-L-phenylalanine succinimide ester (365 mg, 1 mmol) in 15 ml of tetrahydrofuran was allowed to react with phenylhydrazine (260 mg, 2.5 mmol) in 5 ml of tetrahydrofuran for 4 hr at room temperature. The solvent was removed several times with a stream of nitrogen. Water was added to remove N-hydroxysuccinimide, and the product was filtered and dried over P_2O_5 and H_2SO_4 in the vacuum desiccator overnight. Crude product (330 mg, 92%) was obtained. The infrared spectrum and thin layer chromatogram

TABLE IV

Solvent	Temp, °C	Racemization,[a] %	Nucleophile/ oxazolone
Et_2O	0	35	1.1:1
Et_2O	0	75	5:1
THF	0	100	5:1
$CHCl_3$	0	33	1.1:1
$CHCl_3$	25	59	1.1:1

[a] Based on azide run.

showed it to be the desired material, $[\alpha]^{25}D$ −66.6° (*c* 1.5, dimethylformamide).

The succinimide active ester used was 3–4% racemic, $[\alpha]^{25}D$ −51.5° (*c* 1.5, THF). Therefore, the active ester reacted to give phenylhydrazide product with no racemization (compared with the azide method).

Benzoylphenylalaine Dimethylhydrazide. A. From Azide.—The general method used for the preparation of benzoylphenylalanine phenylhydrazide gave 33% crude product on addition of petroleum ether and cooling. Recrystallization from ethyl acetate gave a first crop of 125 mg (21%) of product, mp 202–203°, one spot on tlc, $[\alpha]^{26}D$ −16.9° (*c* 1, dimethylformamide).

Anal. Calcd for $C_{18}H_{21}O_2N_3$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.37; H, 6.73; N, 13.70

B. From Oxazolone.—To 2-phenyl-L-4-benzyloxazolone (1.04 g, 4 mmol) in 15 ml of anhydrous ether was added N,N-dimethylhydrazine (264 mg, 4.4 mmol) (freshly distilled under nitrogen) in 10 ml of ether. After 40 min crystals formed in the flask. After 6 hr (last hour in the refrigerator), 930 mg (75%) of product was filtered off, $[\alpha]^{25}D$ 0° (*c* 1, dimethylformamide). The filtrate had no optical activity. The thin layer chromatogram had one spot which corresponded to the pure product from the azide reaction, and the infrared spectra of the two samples were the same. One recrystallization from ethyl acetate and two from chloroform gave the analytical sample, mp 170–171°.

Anal. Calcd for $C_{18}H_{21}O_2N_3$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.33; H, 6.80; N, 13.42.

Three similar runs were made with freshly distilled $CHCl_3$ (from $CaCl_2$): a 10% excess of dimethylhydrazine was used at 25°; a 10% excess of dimethylhydrazine was used at 0°; and an 8:1 ratio of dimethylhydrazine to oxazolone was used at 25°. All three runs gave the same clearly identifiable product, but in each case with complete racemization.

Benzoylphenylalanine *p*-Nitrophenylhydrazide. A. Attempted Preparation from Azide.—The major product isolated was a yellow, crystalline material, mp 210–212°. The melting point, thin layer chromatogram, infrared spectrum, and nuclear magnetic resonance spectrum did not correspond to material obtained from the oxazolone, mixed anhydride, or indirect approaches. Furthermore, the analysis obtained did not correspond to the desired product, $[\alpha]^{25}D$ −24.3° (*c* 1.5, dimethylformamide).

Anal. Calcd for $C_{22}H_{20}O_4N_4$: C, 65.32; H, 4.99; N, 13.85. Found: C, 63.03; H, 5.19; N, 16.55.

One possibility is the rearrangement of azide to isocyanate, followed by reaction with *p*-nitrophenylhydrazine.

Anal. Calcd for $C_{22}H_{21}N_5O_4$: C, 62.99; H, 5.05; N, 16.69.

B. From Oxazolone.—A solution of *p*-nitrophenylhydrazine (336 mg, 2.2 mmol) in 8 ml of dry tetrahydrofuran was added to 2-phenyl-L-4-benzyloxazolone (502 mg, 2.0 mmol) in 2 ml of tetrahydrofuran at 25°. After 6 hr in the dark, precipitation of product was noted. After 48 hr, the solution was cooled and filtered, giving 435 mg (54%) of a crude yellow solid, $[\alpha]^{25}D$ 0° (*c* 1.5, dimethylformamide). The mother liquor had no optical activity. Two recrystallizations from ethanol gave an analytical sample, mp 226–235°.

Anal. Calcd for $C_{22}H_{20}O_4N_4$: C, 65.32; H, 4.99; N, 13.85. Found: C, 65.43; H, 5.06; N, 13.90.

C. Indirect Route. Procedure 1. Benzyloxycarbonyl-L-phenylalanine *p*-Nitrophenylhydrazide.—A crude product in 71% yield was obtained *via* the dicyclohexylcarbodiimide method. Recrystallization from ethanol gave a first crop of chromatographically pure material in 53% yield, mp 194–197°, $[\alpha]^{25}D$ −8.3° (*c* 2, dimethylformamide).

Procedure 2. L-Phenylalanine *p*-Nitrophenylhydrazide Hydrobromide.—To benzyloxycarbonyl-L-phenylalanine *p*-nitrophenylhydrazide (2.3 g, 5.6 mmol) was added 15 ml of a dry, saturated solution of hydrogen bromide in glacial acetic acid. The mixture was stirred for 3 hr and then added slowly with stirring to 300 ml of cold, anhydrous ether. Crude product (1.75 mg, 85%) was filtered off. Recrystallization from methanol–ether gave a first crop of 1.30 g (63%), $[\alpha]^{25}D$ +48.5° (*c* 1, dimethylformamide).

This material was used directly in the next step without further characterization.

Procedure 3. Benzoylation of L-Phenylalanine *p*-Nitrophenylhydrazide.—To L-phenylalanine *p*-nitrophenylhydrazide hydrobromide (860 mg, 2.35 mmol) in 15 ml of pyridine and 8 ml of dimethylformamide at 0°, benzoyl chloride (316 mg, 2.47 mmol) in 5 ml of ether was added dropwise over 15 min. After 1 hr at 0° and 2 hr at room temperature, the solution was added to 450 ml of 1 *N* hydrochloric acid in the cold. Crude product (560 mg, 63%) was obtained after filtration and washing with water and ether. Recrystallization from ethanol gave a first crop of 300 mg (34%), mp 234–238°, $[\alpha]^{25}D$ −56.8° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{22}H_{20}O_4N_4$: C, 65.32; H, 4.99; N, 13.85. Found: C, 65.16; H, 4.93; N, 13.97.

Benzoyl-L-phenylalanine *o*-Methoxyphenylhydrazide. A. From *o*-Methoxyphenylhydrazine.—*o*-Methoxyphenylhydrazine hydrochloride was added to a saturated sodium bicarbonate solution and the solution was extracted many times with ether. The ether solution was dried over $MgSO_4$ and filtered and the solvent was removed. The hydrazine was distilled at 110° (0.5 mm).

The product solidified rapidly at room temperature and could be handled as a solid, mp 43–44°. This material was used in subsequent reactions.

B. From Oxazolone.—*o*-Methoxyphenylhydrazine (304 mg, 2.2 mmol) in 10 ml of ether was added to 2-phenyl-L-4-benzyloxazolone (502 mg, 2.0 mmol) in 10 ml of ether at 25°. Precipitation of product began within 5 min. After 4 hr, 710 mg (91%) of material was filtered off. No additional material was obtained on evaporation. Thin layer chromatography indicated a single product, $[\alpha]^{25}D$ −43.8° (*c* 1, tetrahydrofuran). Recrystallization from ethyl acetate–hexane gave an analytical sample, mp 186–189°.

Anal. Calcd for $C_{23}H_{23}O_3N_3$: C, 70.93; H, 5.95; N, 10.79. Found: C, 70.85; H, 5.91; N, 10.78.

C. From Azide.—The general procedure described in part A for benzoyl phenylalanine phenylhydrazide was employed. Crude product in 36% yield was obtained by filtration of the reaction mixture after stirring overnight at room temperature. Recrystallization from ethyl acetate–hexane gave pure material in 26% yield, mp 187–188.5°, $[\alpha]^{25}D$ −73.9° (*c* 1, tetrahydrofuran).

Anal. Calcd for $C_{23}H_{23}O_3N_3$: C, 70.85; H, 5.91; N, 10.78. Found: C, 70.97; H, 5.90; N, 10.89.

D. Indirect Method. Procedure 1. Benzyloxycarbonyl-L-phenylalanine *o*-Methoxyphenylhydrazide.—Crude material was obtained in 68% yield by the dicyclohexylcarbodiimide method. Recrystallization from ethyl acetate–hexane gave a pure product, mp 162–165°, $[\alpha]^{25}D$ −22.1° (*c* 2, dimethylformamide). This material was used directly in the next reaction.

Procedure 2. L-Phenylalanine *o*-Methoxyphenylhydrazide Hydrobromide.—The crude material was obtained in 91% yield on treatment of the benzyloxycarbonyl compound with hydrogen bromide in acetic acid. Recrystallization from ethanol–ether gave a first crop in 52% yield, $[\alpha]^{25}D$ −64.7° (*c* 1, dimethylformamide). No attempt was made to recover a second crop. This material was used directly in the next step.

Procedure 3. Benzoylation of L-Phenylalanine *o*-Methoxyphenylhydrazide.—Treatment with benzoyl chloride in a pyridine dimethylformamide mixture gave product in 22% yield after recrystallization from ethanol, mp 185–187°, $[\alpha]^{25}D$ −72.3° (*c* 1, tetrahydrofuran.)

Anal. Calcd for $C_{23}H_{23}O_3N_3$: C, 70.85; H, 5.91; N, 10.78. Found: C, 71.00; H, 5.97; N, 10.84.

Benzoylphenylalanine Hydroxamic Acid.—The procedure of Hurd[39] was used for the preparation of free hydroxylamine. The product was stored under butanol–ether in the refrigerator until use. The material was rapidly filtered, weighed, and dissolved in anhydrous methanol. Aliquot portions were taken from the methanolic solution for each reaction.

A. From Oxazolone.—A solution of hydroxylamine (330 mg, 10.0 mmol) in 10 ml of anhydrous methanol was added to 2-

(39) C. D. Hurd, "Inorganic Syntheses," Vol. 1, McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p 87.

phenyl-L-4-benzyloxazolone (1.0 g, 4.0 mmol) in 20 ml of anhydrous methanol at 0°. After stirring for 12 hr, the solvent was removed in a cold nitrogen stream. A solid product weighing 1.05 g (93%) showing one spot in the thin layer chromatogram was obtained.

Following the reaction with thin layer chromatography indicated that two products had formed initially in a rapid reaction. The material with the greater R_f value in the elution medium (*i.e.*, chloroform) disappeared with time, $[\alpha]^{25}D$ −39.8° (*c* 1, dimethylformamide).

The material was recrystallized from ethyl acetate to give an analytical sample, mp 146–154°.

Anal. Calcd for $C_{16}H_{16}O_3N_2$: C, 67.59; H, 5.67; N, 9.86. Found: C, 67.28; H, 5.47; N, 9.50.

B. From Azide.—The azide reaction was carried out on benzoyl-L-phenylalanine hydrazide (1.1 g, 4 mmol) as previously described in part A for benzoylphenylalanine phenylhydrazide. This time, however, the solid azide product was filtered rapidly, washed with cold saturated potassium chloride solution, and quickly dissolved in 20 ml of cold methylene chloride. After drying over $MgSO_4$, the cold solution was filtered quickly and added to a solution of hydroxylamine (330 mg, 10 mmol) in 20 ml of methanol at 0°. Work-up as previously described gave a crude mixture of several components. The product was obtained in 10% yield on fractionation from chloroform–hexane and ether–petroleum ether. Thin layer chromatography and the infrared spectrum corresponded to material prepared from oxazolone, mp 147–154°, $[\alpha]^{25}D$ −39.7° (*c* 0.5, dimethylformamide).

C. Attempted Preparation from Benzoyl-L-phenylalanine Methyl Ester.—Benzoyl-L-phenylalanine methyl ester (566 mg, 2 mmol) was dissolved in a solution of hydroxylamine (330 mg, 10 mmol) in 20 ml of methanol at 0°. The solution was allowed to stand for 24 hr at 0° and 24 hr at room temperature. Evaporation of the product gave a white solid, which was readily identified as unreacted ester.

Benzoylphenylalanine N-Hydroxypiperidine Ester. A. From Oxazolone.—N-Hydroxypiperidine (202 mg, 2.2 mmol) in 5 ml of anhydrous ether was added to 2-phenyl-L-4-benzyloxazolone (502 mg, 2 mmol) in 10 ml of dry ether at 0°. Precipitation of product began in 3 min. After 2.5 hr at 0°, 620 mg (88.5%) of product was filtered off: $[\alpha]^{25}D$ −25.7° (*c* 2, dimethylformamide). Tlc of the mother liquor did not show additional product. Recrystallization from ether–hexane gave an analytical sample, mp 115–125°.

Anal. Calcd for $C_{21}H_{24}O_3N_2$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.56; H, 6.97; N, 7.88.

B. Determination of Racemization of the Piperidine Active Ester by Conversion into Hydrazide.—To 500 mg of benzoyl phenylalanine N-hydroxypiperidine ester dissolved in 10 ml of boiling methanol, 1 ml of anhydrous hydrazine (large excess) was added. The solution was allowed to cool and stand for 24 hr. The solvent was removed in a stream of nitrogen, and the process was repeated with methanol and then with chloroform. Finally, ether was added and 380 mg of crude product was filtered off (94.7%). Infrared analysis and thin layer chromatography indicated the presence of pure hydrazide. The material was thoroughly dried in a vacuum desiccator over P_2O_5 and H_2SO_4 to remove any traces of hydrazine, $[\alpha]D$ −43.5° (*c* 1, dimethylformamide).

Subsequently, the hydrazine treatment was repeated by dissolving the piperidyl ester in tetrahydrofuran at 0° and adding the hydrazine at 0° in methanol. The product obtained on work-up had the same optical activity as above.

The reaction was repeated twice with a 10% excess of N-hydroxypiperidine in ether at 25° and in tetrahydrofuran at 0°. Similar work-up and conversion of the active ester into benzoyl phenylalanine hydrazide at 0° gave a product, $[\alpha]^{25}D$ −42.0° (c 1, dimethylformamide) for the ether reaction and $[\alpha]^{25}D$ −41.6° (*c* 1, dimethylformamide) for the tetrahydrofuran reaction.

O-(Benzoylphenylalanyl)-N,N-diethylhydroxylamine.—Freshly distilled N,N-diethylhydroxylamine was used in these experiments, bp 40–41° (10 mm).

To 2-phenyl-L-4-benzyloxazolone (502 mg, 2 mmol) in 15 ml of anhydrous ether at 0° was added N,N-diethylhydroxylamine (196 mg, 2.2 mmol) in 5 ml of ether. After 2 hr the solvent was removed under reduced pressure, washed with petroleum ether several times, filtered, washed with water, and dried over P_2O_5 *in vacuo* to give 625 mg (92%) of chromatographically homogeneous material, mp 109–113.5°, $[\alpha]^{25}D$ −21.8° (*c* 1.5, tetrahydrofuran). Recrystallization from ethyl acetate–hexane gave the analytical sample.

Anal. Calcd for $C_{20}H_{24}O_3N_2$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.23; H, 6.74; N, 8.03.

To determine the racemization in the ring-opening reaction, the crude active ester (before recrystallization) was converted into the hydrazide as follows.

To active ester (235 mg, 0.95 mmol) in 5 ml of tetrahydrofuran at 0°, 1 ml of anhydrous hydrazine (large excess) in 5 ml of methanol at 0° was added. Standard work-up afforded 225 mg (79%) of material showing one spot in a thin layer chromatogram. The infrared spectrum confirmed the presence of benzoylphenylalanine hydrazide, $[\alpha]^{25}D$ −26.4° (*c* 1.5, dimethylformamide).

The above reaction was repeated at 25° for 3 hr. Work-up gave 85% active ester, which on reaction with hydrazine gave benzoylphenylalanine hydrazide in 93% yield (based on active ester used), $[\alpha]^{25}D$ −20.1° (*c* 1.5, dimethylformamide).

Repetition of the reaction at 0° for 2 hr and at 25° for 1 hr more gave an 88% yield of active ester, which on reaction with hydrazine gave benzoyl phenylalanine hydrazide in 90% yield (based on active ester used), $[\alpha]^{25}D$ −26.7° (*c* 1.5, dimethylformamide).

Racemization of N,N-Diethylhydroxylamine. Active Ester. A.—A solution of 0.0745 *M* in the active ester of benzoyl-L-phenylalanine and 0.0475 *M* in triethylamine racemized to the extent of 13.5% after 40 hr in tetrahydrofuran at 25°.

B.—A solution 0.0685 *M* in the active ester of benzyloxycarbonyl-L-phenylalanine and 0.0475 *M* in triethylamine under the same conditions as above racemized to the extent of 12.4%.

The racemization in both cases is probably due to direct proton abstraction rather than oxazolone formation. If the latter were the case, the benzoyl derivative should racemize much more readily.

N-Methyl-N-(benzoylphenylalanyl)-O-methylhydroxylamine.—N,O-Dimethylhydroxylamine was prepared by the method of Bissot[40] from the hydrochloride salt.

A. From Oxazolone.—A solution of 2-phenyl-L-benzyloxazolone (502 mg, 2.0 mmol) and N,O-dimethylhydroxylamine (134 mg, 2.2 mmol) in 15 ml of ether at room temperature was allowed to react for 4 hr. Oxazolone could still be noted in the thin layer chromatogram. Cooling of the solution to 0° and filtration gave 520 mg (83.8%) of product, mp 113–114.5°, $[\alpha]^{25}D$ −2.41° (*c* 2.5, tetrahydrofuran). Recrystallization from ether gave an analytical sample, mp 114–115°.

Anal. Calcd for $C_{18}H_{20}O_3N_2$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.64; H, 6.22; N, 9.24.

B. Indirect Procedure.—The product was prepared as described above (part C for benzoylphenylalanine *p*-nitrophenylhydrazide) in 24% overall yield, mp 108.5–111.5°, $[\alpha]^{25}D$ −5.38° (*c* 1.0, tetrahydrofuran).

Anal. Calcd for $C_{18}H_{20}O_3N_2$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.96; H, 6.30; N, 8.47.

Benzoylphenylalanine N-Hydroxysuccinimide Ester. A. From 2-Phenyl-L-4-benzyloxazolone. Procedure 1.—To a solution of 2-phenyl-L-4-benzyloxazolone (502 mg, 2 mmol) in 4 ml of tetrahydrofuran, N-hydroxysuccinimide (253 mg, 2.2 mmol) in 4 ml of tetrahydrofuran was added in one portion and the reaction was allowed to stir for 3 hr at room temperature. The solvent was evaporated at room temperature and 50 ml of water was added to dissolve unreacted N-hydroxysuccinimide. Crude product (530 mg, 73%), showing one spot in thin layer chromatography, was obtained after filtration and washing with cold ether (to remove oxazolone), $[\alpha]^{25}D$ −52.2° (*c* 1.5, tetrahydrofuran).

Procedure 2.—The above reaction was repeated at 0°. After identical work-up, 600 mg (82%) of product was obtained, $[\alpha]^{25}D$ −53.1° (*c* 1.5, tetrahydrofuran).

Procedure 3.—2-Phenyl-L-4-benzyloxazolone (1.0 g, 4 mmol) and N-hydroxysuccinimide (900 mg, 7.8 mmol) were stirred in 10 ml of tetrahydrofuran at 0° for 2 hr and at room temperature for an additional 2 hr. This work-up yielded 1.25 g (86%) of crude material, $[\alpha]^{25}D$ −53.4° (*c* 2, tetrahydrofuran). Recrystallization twice from chloroform gave an analytical sample, mp 164–165°, $[\alpha]^{25}D$ −54.3° (*c* 2, tetrahydrofuran).

Anal. Calcd for $C_{20}H_{18}O_5N_2$: C, 65.52; H, 4.92; N, 7.65. Found: C, 65.41; H, 5.11; N, 7.64.

B. Determination of Optical Purity of Succinimide Active

(40) T. C. Bissot, R. W. Parry, and D. H. Campbell, *J. Amer. Chem. Soc.*, **79**, 796 (1957).

Ester.—To a solution of benzoylphenylalanine N-hydroxysuccinimide ester (240 mg, 0.66 mmol) in 20 ml of tetrahydrofuran at 0°, hydrazine hydrate (150 mg, 3 mmol) in 5 ml of methanol was added at 0°. Precipitation of product was noted immediately. After 2 hr, the solvent was removed under a stream of nitrogen at room temperature. After addition of water to remove N-hydroxysuccinimide, filtration, and drying over P_2O_5, 160 mg (85%) of chromatographically pure paterial was obtained, $[\alpha]^{25}D$ −45.7° (c 1, dimethylformamide).

C. Racemization by Methanol.—Benzoyl-L-phenylalanine succinimide ester (250 mg) was boiled in 20 ml of methanol for 20 min. Evaporation of solvent gave completely racemized starting material as determined by infrared spectroscopy thin layer chromatography, and polarimetry. No methanolysis took place under these conditions.

Benzyloxycarbonyl-L-phenylalanine Succinimide Ester.—The crude product was obtained in 68% yield by the dicyclohexylcarbodiimide method. Recrystallization from ethyl acetate–hexane gave a first crop of 1.3 g (45%) of crystalline material, mp 136–138.5°, $[\alpha]^{25}D$ −21.5° (c 1.5, tetrahydrofuran).

Anal. Calcd for $C_{21}H_{20}O_6N_2$: C, 63.63; H, 5.08; N, 7.07. Found: C, 63.53; H, 5.33; N, 6.93.

Racemization by Methanol.—The succinimide active ester (250 mg) was boiled for 20 min in methanol and then the solvent was removed at room temperature. The product was washed with hexane and filtered. Infrared and thin layer analyses showed no methanolysis, $[\alpha]^{25}D$ −19.4° (c 1.5, tetrahydrofuran).

Instruments and Apparatus.—All measurements of optical activity were made on a Model 80 Rudolph polarimeter equipped with a Model 200A oscillating polarizer. Monochromatic light was obtained by a prism monochromator equipped with an independent Xenon light source (Hanovia 901B). Center-fill, 2-dm polarimeter tubes with a bore of 3 mm in diameter were used (Polarimeter tube type 14, catalogs of O. C. Rudolph and Sons, Caldwell, N. J.). The temperature of the tube compartment was kept constant at 25 ± 0.2° by a circulating pump connected to a constant-temperature bath. The voltage applied to the photoelectric cell was controlled by a Keithley Voltage Supply Model 240.

High-resolution nuclear magnetic resonance spectral measurements were made with the Cary A-60 megacycle instrument at room temperature and resonances are expressed in units relative to tetramethylsilane as an internal standard.

Infrared spectra were determined with a Perkin-Elmer Model 132, 21, or 521 spectrophotometer from Nujol mulls or potassium bromide pellets.

Registry No.—2-Phenyl-L-4-benzyloxazolone, 5874-61-3; benzoyl-L-phenylalanine methyl ester, 3005-61-6; benzoyl-L-phenylalanine hydrazide, 23912-50-7; benzoylphenylalanine *t*-butyloxycarbonyl hydrazide, 23912-51-8; benzoylphenylalanine phenylhydrazide, 23912-53-0; benzoylphenylalanine dimethylhydrazide, 23912-54-1; benzoylphenylalanine *p*-nitrophenylhydrazide, 23912-55-2; benzoyloxycarbonyl-L-phenylalanine *p*-nitrophenylhydrazide, 23912-56-3; L-phenylalanine *p*-nitrophenylhydrazide hydrobromide, 23912-57-4; benzoyl-L-phenylalanine *o*-methoxyphenylhydrazide, 23912-58-5; benzoyloxycarbonyl-L-phenylalanine *o*-methoxyphenylhydrazide, 23912-59-6; L-phenylalanine *o*-methoxyphenylhydrazide hydrobromide, 23912-60-9; benzoylphenylalanine hydroxamic acid, 23912-61-0; benzoylphenylalanine N-hydroxypiperidine ester, 23967-35-3; *o*-(benzoylphenylalanyl)-N,N-diethylhydroxylamine, 23912-62-1; N-methyl-N-(benzoylphenylalanyl)-O-methylhydroxylamine, 23912-63-2; benzoylphenylalanine N-hydroxysuccinimide ester, 23912-64-3; benzyloxycarbonyl-L-phenylalanine succinimide ester, 3397-32-8.

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Reaction of Aldehydes with N-Hydroxybenzenesulfonamide. Acetal Formation Catalyzed by Nucleophiles

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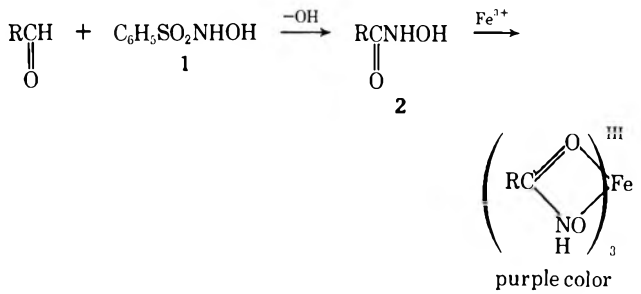
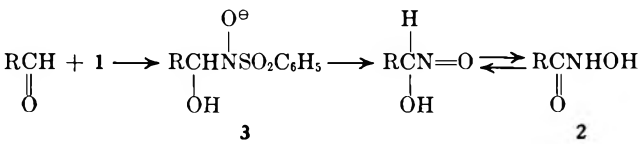
The reaction of N-hydroxybenzenesulfonamide (1) with aldehydes was studied. In the presence of strong base, hydroxamic acids are formed. In methanol in the absence of base, rapid acid catalysis by 1 takes place, leading to dimethyl acetals. In this manner acetal formation or hydrolysis can be catalyzed by the mild acids 1 or its O-benzyl ether 6. Treatment of 1 or 6 with base does not appear to furnish nitrenes, as indicated by lack of reaction with olefins.

The reaction of aldehydes with N-hydroxybenzenesulfonamide (1) under basic conditions constitutes the basis for a well-known spot test used in the qualitative identification of aldehydes.[1] This test, known as the Angeli–Rimini test, involves the formation of a hydroxamic acid 2 which forms characteristically colored complexes with ferric ions.[2]



A proposed mechanism for hydroxamic acid formation involves the following scheme.[3] Alternatively, 1,2 elimination of benzenesulfinic acid from **3** would lead to **2**.



Since α-elimination reactions have been used to generate nitrenes,[4] we considered the possibility that the

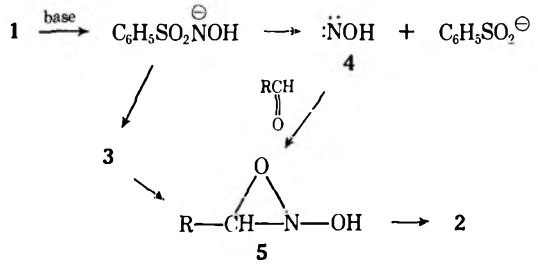
(1) F. Feigl, "Spot Tests In Organic Chemistry," 2nd ed, Elsevier Publishing Co., New York, N. Y., 1966, p 196.

(2) A. Angeli, *Gazz. Chim. Ital.*, **26** (II), 17 (1896); E. Rimini, *ibid.*, **31** (II), 84 (1901).

(3) P. A. S. Smith and G. E. Hein, *J. Amer. Chem. Soc.*, **82**, 5732 (1960).

(4) W. Lwowski, *Angew. Chem., Int. Ed. Engl.*, **6**, 897 (1967); D. Carr, T. P. Seden, and R. W. Turner, *Tetrahedron Lett.*, 477 (1969).

above reaction may involve the intermediacy of an N-hydroxynitrene **4** which attacks the carbonyl group to give **5**. Alternately, nucleophilic attack of the anion of **1** on the C=O could take place followed by ring closure to an N-hydroxyoxaziridine **5** which would ring open to **2**. Our past interest in the introduction of nitrogen functions into organic molecules[5] and in small-ring heterocycles[6] suggested a study of the reaction of N-hydroxybenzenesulfonamide (**1**) with C=O and C=C systems. During this study we discovered a facile synthesis and hydrolysis of acetals catalyzed by **1**.



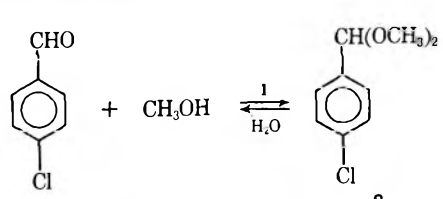
Results and Discussion

We were able to confirm the fact that aldehydes react with **1** in the presence of NaOH in ethanol–water or DMSO or even better with $NaOCH_3$ in methanol to produce hydroxamic acids **2** in fair to good yields. Acidic work-up furnished benzenesulfinic acid as a by-product in 96% yield. Ketones react much slower under these reaction conditions and lead in poor yield to N-hydroxyamides.[7]

Attempts to add **4** to olefins such as cyclohexene or dihydropyran by treatment with **1** or its O-benzyl ether

$C_6H_5SO_2NHOCH_2C_6H_5$
6

6 with various bases were unsuccessful. Unexpectedly, we found that slow addition of sodium methoxide in methanol to a solution of *p*-chlorobenzaldehyde (**7**) and N-hydroxybenzenesulfonamide (**1**) in methanol gave rise to the dimethyl acetal **8** in good yield. It soon became obvious that aldehydes reacted readily with methanol in the presence of 1 equiv of **1** within 10–15 min at room temperature even in the absence of sodium methoxide to form dimethyl acetals (see Table I). This was surprising since the pK_a of **1** is approximately 9.[8] We were able to show that N-hydroxybenzenesulfonamide (**1**) as well as its ether **6** behave as powerful nucleophilic catalysts in this reaction.



(5) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967); A. Hassner and F. Boerwinkle, *J. Amer. Chem. Soc.*, **90**, 216 (1968), and references cited therein.

(6) A. Hassner and F. W. Fowler, *ibid.*, **90**, 2869 (1968); A. Hassner, G. J. Mathews, and F. W. Fowler, *ibid.*, **91**, 5046 (1969).

(7) L. Panizzi, G. diMaio, P. A. Tardella, and L. D'Abbiers, *Ric. Sci., Parte 2, Sez. A*, **31**, 312 (1961).

(8) O. Exner and W. Simon, *Collect. Czech. Chem. Commun.*, **30**, 4079 (1965).

TABLE I

FORMATION OF DIMETHYL ACETALS WITHIN 15 MIN IN METHANOL IN THE PRESENCE OF 1 EQUIV OF 1

Aldehyde	% yield of acetal[a]
Benzaldehyde	87
p-Chlorobenzaldehyde (**7**)	85
p-Methylbenzaldehyde	86
p-Methoxybenzaldehyde	77
2,4,6-Trimethylbenzaldehyde	45
p-Dimethylaminobenzaldehyde	
1-Heptanal	89
Cinnamaldehyde	85
Cyclohexanone	75
Benzyl methyl ketone	33

[a] Usually determined from the nmr spectrum of the crude product. In the case of **7**, the acetal was isolated and compared with authentic sample.

Neither benzenesulfonamide nor other weak acids such as phenols catalyze the acetal formation. Acetic acid, a much stronger acid ($pK_a = 4.75$) is considerably poorer than **1** in catalyzing acetal formation (see Table II). The effectiveness of **1** as a catalyst in acetal

TABLE II

EFFECT OF ACIDS ON DIMETHYLACETAL FORMATION FROM *p*-CHLOROBENZALDEHYDE (**7**) IN METHANOL AT 25°

Acid (equiv)[a]	pK_a	Reaction time, min	% yield[b] **7**	% yield[b] **8**
HCl (1.0)	<1	15		85
HCl (0.1)	<1	15		80
Acetic acid (1.0)	4.75	15	95	5
		60	86	12
p-Nitrophenol (1.0)	6.85	15	79	
1 (1.0)	9.26	15		80
1 (0.1)	9.26	15	11	89
6 (1.0)	~9	15	24	68
Phenol (1.0)	9.85	15	80	
Benzenesulfonamide (1.0)	>10	2,400	89	
2-Pyridone (1.0)		15	90	

[a] All reactions were carried out and worked up as described for the use of **1**. [b] The yields were calculated from the nmr spectrum of the crude product.

production appears comparable with that of hydrochloric acid and 0.1 equiv of the **1** is sufficient to accomplish dimethyl acetal formation within 15 min. That this mild acid serves only in a catalytic capacity can be shown by the recovery of N-benzyloxybenzenesulfonamide (**6**) in 94% yield after assuming its role in the conversion of *p*-chlorobenzaldehyde to its acetal **8** in 85% yield.

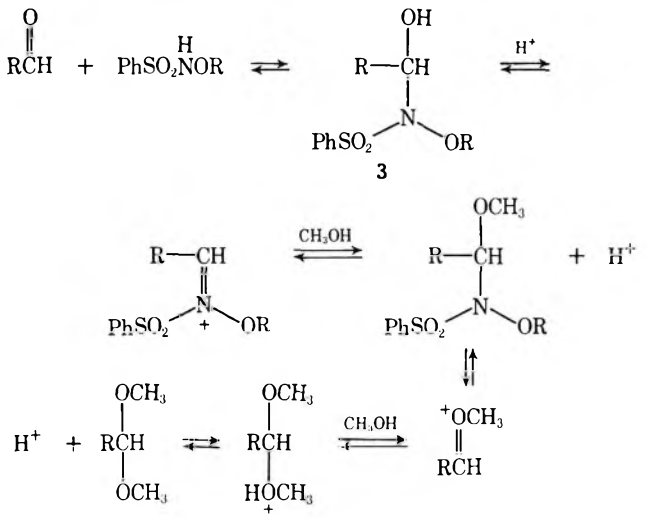
N-Hydroxybenzenesulfonamide (**1**) also serves as a mild acid catalyst in the hydrolysis of **8** to **7** in dioxane–water at 25°. The reagent **1** is stable to methanol but unstable to base at room temperature and is converted to benzenesulfinic acid (isolated) and nitrous oxide. The latter was identified by mass spectrometry.

The conversion of ketones to dimethyl ketals in the presence of **1** is slower than that of aldehydes. Cyclohexanone and benzyl methyl ketone gave dimethyl ketals in 75 and 33% yield, respectively, but cyclopentanone did not react within 15 min.

Aldehydes that contain basic functions, such as *p*-dimethylaminobenzaldehyde and 3-pyridinecarboxaldehyde, do not give acetals under the conditions mentioned.

Though the exact nature of the function of **1** or **6** are not yet understood, the acid catalysis must involve assistance by the N oxygen and is probably related to the strong nucleophilic character of **1**. Nucleophiles with an electronegative atom adjacent to the nucleophilic atom, such as hydroxylamine or hydrazine, are unusually efficient nucleophiles toward carbonyl groups.[9]

A plausible pathway in which **1** or **6** acts as a good nucleophile as well as a good leaving group is suggested below. It also explains the unexpected formation of acetals from methanol and aldehydes in the presence of hydroxylamine–hydroxylamine hydrochloride buffer.[10] In the presence of strong base, loss of benzenesulfinic acid from **3** leads to formation of hydroxamic acids.



An alternative mechanism in which **1** or **6** act as an acid and a base is unlikely since 2-pyridone, which can act in this manner,[11] does not catalyze acetal formation. On the other hand, hydroxylamine and its derivatives have been reported to catalyze hydrolysis of esters by attack on the carbonyl group.[12]

Experimental Section

Formation of *p*-Chlorobenzenehydroxamic Acid.—To an ice-cooled solution of 365 mg (2.1 mmol) of N-hydroxybenzenesulfonamide (**1**) in methanol, 2.18 ml (4.2 mmol) of a 1.93 *M* sodium methoxide–methanol solution was added dropwise with stirring. Then 281 mg (2 mmol) of *p*-chlorobenzaldehyde (**7**) dissolved in 2 ml of methanol was added, and the reaction mixture was warmed to room temperature and stirred an additional 2 hr. The solution was concentrated under vacuum, diluted with 100 ml of ether, and extracted twice with 2 *M* NaOH. The organic phase yielded 45 mg (16%) of slightly impure starting material. The aqueous phase was acidified with concentrated HCl to pH 7–8 and extracted twice with ethyl acetate. The dried solution ($MgSO_4$) was concentrated giving 225 mg (68%) of *p*-chlorobenzenehydroxamic acid: mp 193–195° dec; ir (KBr) 3250 (N—H), 2700 (broad, O—H), 1600 (C=O), 1550, 1090, 895, 845 cm^{-1}; nmr DMSO-d_6 τ 2.8 (broad, s, 1), 0.65 (broad, s, 1), 2.34 (m, 4).

If the reaction was carried out using 2 equiv of 2 *N* NaOH in ethanol–water (2:1), 35% pure hydroxamic acid was obtained together with of a mixture of **7** and its acetal **8** (*ca.* 45%).

Using DMSO–water (1:1) instead of ethanol–water as a solvent system led to isolation of 15% **7** and 82% *p*-chlorobenzenehydroxamic acid, mp 193–195° dec, lit.[13] mp 185°.

Acid-Catalyzed Formation of *p*-Chlorobenzaldehyde Dimethyl Acetal (8).—A solution of 281 mg (2 mmol) of *p*-chlorobenzaldehyde (**7**) and 365 mg (2.1 mmol) of N-hydroxybenzenesulfonamide (**1**) in 8 ml of absolute methanol was let stand for 15 min at room temperature, diluted with 50 ml ether, and extracted two times with 10 ml of 2 *M* NaOH solution. The ethereal extract was washed twice with NaCl solution, dried ($MgSO_4$), and concentrated giving 298 mg [bp 104–106° (0.2 mm), lit.[14] bp 125.5°–126.5° (35 mm) (80%)] of the dimethyl acetal **8**: nmr $CDCl_3$ τ 2.61 (s, 4), 4.64 (s, 1), 6.70 (s, 6); mass spectrum (70 eV) *m/e* (relative intensity) 188 (2) and 186 (6) for M^+, 157 (33) and 155 (100) for M − OCH_3, 141 (8) and 139 (25) for M − 47, 113 (6) and 111 (18) for M − $HC(OCH_3)_2$, 91 (35).

Acid-Catalyzed Hydrolysis of 8.—A solution of 2 mmol of acetal **8** and 2 mmol of **1** in 40 ml of dioxane–water (1:1) was allowed to stand for 5 hr at 25°. Work-up gave *p*-chlorobenzaldehyde (**7**) in nearly quantitative yield identified by ir and nmr.

Reactivity of N-Hydroxybenzenesulfonamide (1). A. Reaction with Sodium Methoxide.—To a solution of 346.4 mg (2 mmol) of **1** in 5 ml of methanol was added 113 mg (0.21 mmol) of $NaOCH_3$ at room temperature with stirring. A precipitate of colorless crystals appeared which dissolved after about 30 min. After another 2 hr the methanol was evaporated giving colorless crystals of sodium benzenesulfinate. This salt was acidified with 2 *N* HCl, and the benzenesulfinic acid was extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and concentrated giving 209 mg (74%) of benzenesulfinic acid: mp 81–83° (lit.[15] 85°); ir $CHCl_3$ 2500 (broad, O—H), 1090 cm^{-1} (S=O).

B. Reaction with Methanol.—N-Hydroxybenzenesulfonamide (**1**) was recovered unchanged upon standing in methanol (0.25 *M* solution) for 1 hr at 25°. After 45 hr impure **1** was recovered.

Reaction of 7 with N-Benzoxybenzenesulfonamide (6).—A solution of 281 mg of *p*-chlorobenzaldehyde (**7**) and 1 equiv of **6** in methanol was allowed to stand for 30 min and worked up as described under formation of acetal **8**. The neutral fraction consisted of 85% **8** and 15% **7** as indicated by nmr. From the basic fraction there was isolated N-benzoxybenzenesulfonamide (**6**), 94% yield, mp 103–105°.

Registry No.—**1**, 599-71-3; **7**, 104-88-1; benzaldehyde, 100-52-7; *p*-methylbenzaldehyde, 104-87-0; *p*-methoxybenzaldehyde, 123-11-5; 2,4,6-trimethylbenzaldehyde, 487-68-3; *p*-dimethylaminobenzaldehyde, 100-10-7; 1-heptanol, 111-71-7; cinnamaldehyde, 104-55-2.

Acknowledgment.—Support of this work by Grant GP 8675 from the National Science Foundation and PRF Grant A2004-A1,4 from the American Chemical Society is gratefully acknowledged. We are grateful to Professor R. E. Barnett, University of Minnesota, for helpful discussions.

(9) W. P. Jencks and J. Carriulo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960).
(10) T. Sasaki and T. Yoshioka, *Tetrahedron Lett.*, 827 (1968).
(11) *Chem. Eng. News*, **47**, 74 (Oct 13, 1969).
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Bridgehead Nitrogen Heterocycles. III. The 3H-[1,2,4]Thiadiazolo[4,3-*a*]pyridine System[1]

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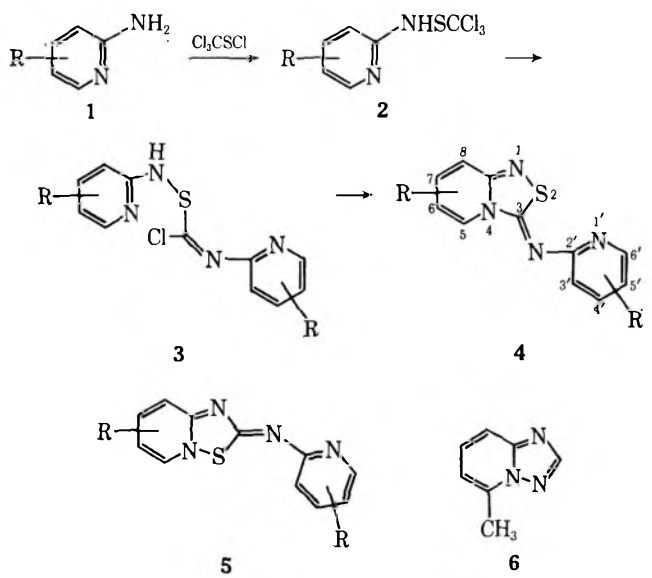
Reaction of 2-aminopyridines with perchloromethyl mercaptan in the presence of base gave 3-(2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridines, a new heterocyclic ring system.

The 1,2,4-thiadiazole ring system, one of the more interesting heterocyclic systems, has been the subject of numerous investigations.[2] A synthetic procedure of considerable utility is the formation of the ring system from amidines and perchloromethyl mercaptan (trichloromethanesulfenyl chloride) developed by Goerdeler,[3] and our interest in bridgehead nitrogen ring systems led us to apply this method to the synthesis of ring-fused 1,2,4-thiadiazoles. There are only two reported examples of ring-fused 1,2,4-thiadiazoles, a [1,2,4]thiadiazolo[4,5-*a*]pyrimidine derivative[4] and a [1,2,4]thiadiazolo[3,4-*b*]benzothiazole derivative.[5]

It was anticipated that the most direct route to the [1,2,4]thiadiazolo[4,3-*a*]pyridine system would be from 2-aminopyridine (**1**, R = H) and perchloromethyl mercaptan. An earlier report[6] described these two reactants as yielding 2-trichloromethylthioaminopyridine (**2**, R = H) which did not undergo ring-closure reactions to bicyclic products. Variation of the reaction conditions as described below led to a cyclization product to which structure **4** (R = H) has been assigned. Structure **5**, resulting from initial condensation at the pyridine nitrogen atom, may be excluded from consideration on the basis of the following data.



Analytical data and molecular weight data (Table I) clearly establish that ring closure occurred. Structure **4** is preferred over that resulting from the alternative mode of ring closure, represented by structure **5**, on spectroscopic and chemical grounds. In bridgehead nitrogen heterocycles of this type,[7] a heteroatom in the five-membered ring adjacent to the bridgehead nitrogen atom has a pronounced effect on the chemical shift of the proton, and substituents, in the *peri* position; *e.g.*, in the *s*-triazolo[1,5-*a*]pyridine system[7a] (**6**) the chemical shift of the 5 proton is τ 1.38 and that of a 5-methyl substituent is τ 7.24, whereas in the indolizine system[7b] the corresponding chemical shifts are τ 1.91 and 7.59, respectively. In the nmr spectra of these cyclization products (Table II), the chemical shift of the 5 proton is τ 1.75 and that of a 5-methyl substituent is τ 6.89, data consistent with structure **4**, in which the shielding is due to the 2-pyridylimino substituent in the 3 position. The synthesis of **4** (R = H) from 2-trichloromethylthioaminopyridine (**2**, R = H) and 2-aminopyridine confirmed the above assignment.

TABLE I

PRINCIPAL IONS PRESENT IN THE MASS SPECTRA OF REPRESENTATIVE 3-(2-PYRIDYLIMINO)-3H-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINES[a]

Compd no.	*m/e*[b] (relative abundance)
1	228 (42), 227 (12), 136 (18), 124 (27), 78 (100), 51 (31)
2	257 (18), 256 (100), 255 (20), 150 (50), 138 (55), 92 (78)
7	300 (22), 299 (20), 298 (38), 297 (12), 296 (50), 295 (25), 170 (17), 160 (32), 158 (82), 114 (32), 112 (100), 76 (82)
11	365 (19), 364 (100), 363 (24), 362 (100), 245 (11), 244 (24), 243 (10), 242 (34), 182 (10), 181 (10), 151 (33), 106 (100), 79 (35), 78 (35)

[a] Appropriate metastable transitions were observed for the main fragmentations. [b] Ions with a relative abundance >10% only are reported.

The nmr data (Table II) for various derivatives of this ring system are consistent with those for similar heterocycles. Ring coupling constants (determined by first-order analysis) and the *ortho* benzylic coupling constants indicate that considerable bond fixation might be present in this system.

The ring system **4** was stable to hot, dilute acid or base, and no oxidation was observed with excess 30% hydrogen peroxide in acetic acid. Sodium metaperio-

(1) (a) Financial support of this work by U. S. Publich Health Service Research Grant No. CA-08495, National Cancer Institute, is gratefully acknowledged. (b) Abstracted in part from the Ph.D dissertation of R. A. to be submitted to the Graduate School, Rensselaer Polytechnic Institute. (c) National Dairy Fellow, 1969. (d) Part II: K. T. Potts and U. P. Singh, *Org. Mass Spectrom.*, in press.

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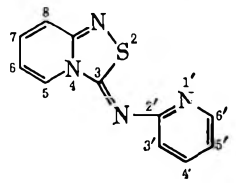
TABLE II

CHEMICAL SHIFTS (τ UNITS) AND COUPLING CONSTANTS (HERTZ) FOR VARIOUS 3H-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINE DERIVATIVES[a]



Compd no.	τ_5	τ_6	τ_7	τ_8	$\tau_{3'}$	$\tau_{4'}$	$\tau_{5'}$	$\tau_{6'}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{3,8}$	$J_{7,8}$
1[b]	1.75	3.15	m[c]	m	m	m	m	2.55	7.2	1.2	1.2	6.4	1.4	
2[d]	*6.89*[e]	3.91	2.40	3.0[f]	3.0[f]	3.0[f]	3.0[f]	*7.33*[e]	1.0			7.0	1.4	7.0
3[d]	1.75	*7.77*[e]	2.45	2.60	2.85[f]	2.85[f]	*7.67*[e]	1.60	1.4					7.0
7[b]	2.35		3.15[f]	3.15[f]	3.15[f]	3.15[f]		2.07		2.0				
8[b]	1.24		1.82	2.37	2.6[f]	2.6[f]		0.94		2.0				9.0
4[d]	1.67[g]	3.52	*7.70*[e]	2.82	3.15[f]	*7.60*[e]	3.15[f]	1.67[g]	7.2		*h*		1.4	1.0
6[d]	*6.95*[e]	4.15	*7.90*[e]	3.12	3.30	*7.75*[e]	3.45	*7.45*[e]	1.0				1.3	1.3
5[d]	1.75[g]	3.68	2.60	*7.62*[e]	*7.55*[e]	3.15[f]	3.15[f]	1.75[g]	7.3	nr		7.3		1.0
9	1.70	2.70	m[i]	m	m	m		1.85	7.2	1.2	1.2	6.4	1.4	
10	1.40	*7.50*[e]	1.95	2.40		2.10	*7.50*[e]	1.50	1.0	1.0	*h*			
11	*6.70*[e]	3.28	*7.55*[e]	2.55	2.82	*7.41*[e]		*7.12*[e]	1.0					1.3

[a] Spectra were determined using TMS as internal reference except for compound 1 where DSS was used. [b] Determined in CF_3CO_2H. [c] m, very broad overlapping multiplet between τ 1.75 and 3.15. [d] Determined in $CDCl_3$. [e] Methyl resonances italicized. [f] Center of overlapping multiplet. [g] Overlapping multiplet. [h] Not resolvable. [i] Broad overlapping multiplet between τ 1.70 and 2.70.

TABLE III

SOME 3-(1-METHYL-2-PYRIDYLIMINO)-3H-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINIUM IODIDES

Salt derived from compd no.	Mp, °C	Yield, %	Color[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	214–216	85	Lime green	$C_{12}H_{11}IN_4S \cdot H_2O$[b]	37.12	3.37	14.30	37.92	3.20	14.58
2	240–242	90	Yellow	$C_{14}H_{15}IN_4S$[c]	42.22	3.80	14.07	42.28	3.86	14.06
5	237–238	95	Yellow	$C_{14}H_{15}IN_4S$[d]	42.22	3.80	14.07	42.48	3.78	14.23
4	257–259	90	Orange	$C_{14}H_{15}IN_4S$[e]	42.22	3.80	14.07	42.28	3.67	13.93
6	245	95	Orange	$C_{16}H_{19}IN_4S$[f]	44.97	4.72	13.11	44.94	4.66	12.90

[a] Needles. [b] Registry no. 24097-61-8. [c] 24097-62-9. [d] 24215-63-2. [e] 24097-63-0. [f] 24097-64-1.

date, specific for the oxidation of sulfides to sulfoxides,[8] was also without effect. No reaction was observed with dienophiles such as maleic anhydride and dimethyl acetylenedicarboxylate. Quaternization of **4** occurred sluggishly with methyl iodide at the pyridine nitrogen atom. These salts, described in Table III, are all highly colored, stable products. The nmr spectrum of the methiodide of compound **1** was consistent with alkylation occurring at the position shown. Alkylation at N-1 would have resulted in a considerable upfield shift[9] of the 8 proton, whereas the spectral pattern of the protons at the 5, 6, 7, and 8 positions was very similar to that of the parent system. Also the ultraviolet spectra of the methiodides were practically superimposable on those of the appropriate precursors, providing additional support for methylation at the pyridine nitrogen atom.

Bromination of **4** occurred readily with bromine in glacial acetic acid. Nmr data (Table II) showed that in these bromo products (Table IV) substitution had occurred in the 3-pyridyl substituent. This was confirmed by the synthesis of 3-(5-bromo-2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridine from **2** and 2-amino-5-bromopyridine. Introduction of methyl substituents into the π moiety of the fused system did not alter the bromination pattern and, with the 5,7-dimethyl derivative of **4**, a small amount of dibromo substitution in the 3 substituent was observed.

Several spectral characteristics are worthy of mention. In addition to the infrared >C=N– absorption at *ca.* 1640 cm^{-1} (Table IV), there was always present a characteristic absorption in the region of 1430–1460 cm^{-1}. A similar absorption has been attributed[10] to a 1,2,4-thiadiazole ring deformation and, in this present series, we have found this absorption band to be of diagnostic value. Table I illustrates, for representative 3-(2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridines, the two main fragmentation patterns observed in their mass spectra. The molecular ion fragments by breaking of the C_3–N_4 bond and either the N_1–S or the C_3–S bond. In the former case, the π moiety of the fused system is eliminated as a neutral fragment; in the latter case, 2-pyridyl isocyanide is eliminated. Several other fragmentation pathways, consistent with the variety of substituents in the fused nucleus (Table IV), were observed to a minor degree. An interesting feature of the spectra of the bromo-substituted compounds was the presence of a doubly charged molecular ion whose intensity was dependent on the number of bromo substituents.

The ultraviolet absorption spectral data listed in Table IV also reveal some interesting information about

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(9) W. W. Paudler and L. S. Helmick, *J. Heterocycl. Chem.*, **5**, 691 (1968).
(10) J. Goerdeler and M. Budnowski, *Chem. Ber.*, **94**, 1382 (1961).

TABLE IV

SOME DERIVATIVES OF THE 3H-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINE SYSTEM (**4**)[a]

Compd no.	R	3-Pyridylimino substituent	Mp, °C	Color[b]	Yield, %	Uv data, λ_{max}, nm (log ϵ)	Ir data, $\nu_{C=N}$, cm^{-1}
1	H	H	174–176	A	75	392 (4.00), 378 (4.03), 338 (4.43), 328 (4.20), 280 (4.08), 240 (4.26)	1640
2	5-CH_3	6′-CH_3	173	B	85	395 (3.75), 380 (3.81), 347 (4.16), 337 (3.97), 280 (3.69), 230 (4.08)	1630
3	6-CH_3	5′-CH_3	194–196	C	65	395 (3.93), 380 (3.96), 343 (4.28), 333 (4.17), 285 (4.09), 245 (4.26)	1645
4	7-CH_3	4′-CH_3	189–191	C	80	375 (4.78), 365 (4.79), 323 (5.06), 312 (4.97), 270 (4.82), 228 (5.09)	1640
	7-CH_3	4′-CH_3	228[c]	D	90	370 (3.93), 328 (4.17), 318 (4.09), 273 (3.94), 238 (4.23)	1630
5	8-CH_3	3′-CH_3	150–151	D	85	390 (4.01), 375 (3.99), 339 (4.17), 327 (4.08), 277 (3.90), 230 (4.11)	1630
6	5,7-$(CH_3)_2$	4′,6′-$(CH_3)_2$	164–165	A	80	380 (4.28), 343 (4.53), 330 (4.40), 275 (4.15), 230 (4.52)	1640
7	6-Cl	5′-Cl	205–207	D	35	405 (3.82), 387 (3.88), 348 (4.34), 336 (4.23), 288 (4.17), 250 (4.32), 225 (4.26)	1640
8	6-Br	5′-Br	230–232	D	40	408 (4.05), 388 (4.11), 348 (4.46), 337 (4.37), 290 (4.37), 252 (4.45)	1620
9	H	5′-Br	172-174	D	90	393 (4.06), 377 (4.08), 347 (4.22), 290 (4.07), 240 (4.28), 225 (4.32)	1640
10	6-CH_3	3′-Br,5′-CH_3	224–225	D	90	395 (3.98), 378 (4.00), 348 (4.18), 293 (3.98), 242 (4.17)	1650
11	5,7-$(CH_3)_2$	5′-Br,4′,6′-$(CH_3)_2$	213–214	D	85	390 (4.04), 378 (4.07), 348 (4.22), 280 (3.90), 240 (4.24)	1650
12	5,7-$(CH_3)_2$	3′,5′-$(Br)_2$,4′,-6′-$(CH_3)_2$	270	D		395 (4.09), 380 (4.11), 348 (4.37), 337 (4.22), 288 (3.99), 247 (4.28), 230 (4.31)	1640

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds in this table. [b] Needles: A, rust; B, gold; C, orange; D, yellow. [c] Perchlorate.

this ring system. The absorptions can be divided into four general bands. The first band, centered around 390 nm, is assigned to the ring-fused portion of the molecule. The second, and the most structured band, occurs at about 340–350 nm while a third band occurs at about 280–290 nm. These last two bands are assigned to the exocyclic π moiety, substitution of bromine into the 5 position of the exocyclic π moiety causing a strong shift in the second and third bands without affecting the first band. Furthermore, a bromine substituent in the 6 position of the fused-ring system shifts the first band while leaving the second and third bands unaffected. It was observed that the second band lost most of its fine structure when the exocyclic π moiety contained either methyl, bromine, or chlorine substituents, and this change was of considerable help in structural assignments. The fourth band centered at 240–250 nm was also assigned to the ring-fused portion of the system. It shifted only on introduction of substituents into the thiadiazolo[4,3-*a*]pyridine nucleus.

The formation of compound **9** from **2** and 2-amino-5-bromopyridine indicates that the fused-ring system is most likely formed *via* the intermediates **2** and **3**. As **3** is an imidoyl chloride, it would be expected to undergo an extremely facile ring closure to **4**.

Experimental Section[11]

General Procedure for the Preparation of 3-(2-Pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridines.—The aminopyridine (0.04 mol) in chloroform (200 ml) and Et_3N (0.1 mol) were stirred at 0° while Cl_3CSCl (3.6 g, 0.02 mol) was added dropwise over 1 hr. After the mixture was stirred at room temperature for 3 hr, the solvent was removed and the residue was washed with methanol. Crystallization from acetone (for the Br derivative chloroform was used) afforded the products described in Table IV.

(11) All evaporations were done under reduced pressure using a Rotavap apparatus. Spectral characterizations were performed with the following instrumentation: ir and uv spectra, Perkin-Elmer Model 337 and Cary Model 14 spectrophotometers, respectively; nmr, Varian A-60 spectrometer; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer. Melting points were taken in capillaries and microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn.

General Procedure for the Preparation of 3-(1-Methyl-2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridinium Iodides.—A 1:1 mixture of the above bases and CH_3I was refluxed in chloroform. The salt crystallized from the hot reaction mixture and, on recrystallization from ethanol, gave the products described in Table III.

Bromination of 3-(2-Pyridylimino)-3H-[1,2,4]thiadiazolo-[4,3-*a*]pyridines.—The fused-ring system (0.02 mol) in glacial acetic acid (200 ml) was stirred at room temperature while a solution of Br_2 (0.02 mol) in glacial acetic acid (10 ml) was added slowly. An immediate reaction occurred and the reaction mixture was heated at 100° for 1 hr during which time it became a bright yellow color. The reaction mixture was poured over ice and the precipitate recrystallized from acetone.

Registry No.—**1**, 24097-57-2; **2**, 24097-94-7; **3**, 24097-95-8; **4**, 24097-96-9; **4** (perchlorate), 24097-74-3; **5**, 24162-35-4; **6**, 24097-97-0; **7**, 24097-98-1; **8**, 24097-99-2; **9**, 24162-36-5; **10**, 24097-58-3; **11**, 24097-59-4; **12**, 24097-60-7.

Thiapyrone Chemistry. III.[1] The Reaction of 2,6-Dimethylthio-3,5-diphenylthiapyrone with Hydroxide Ion

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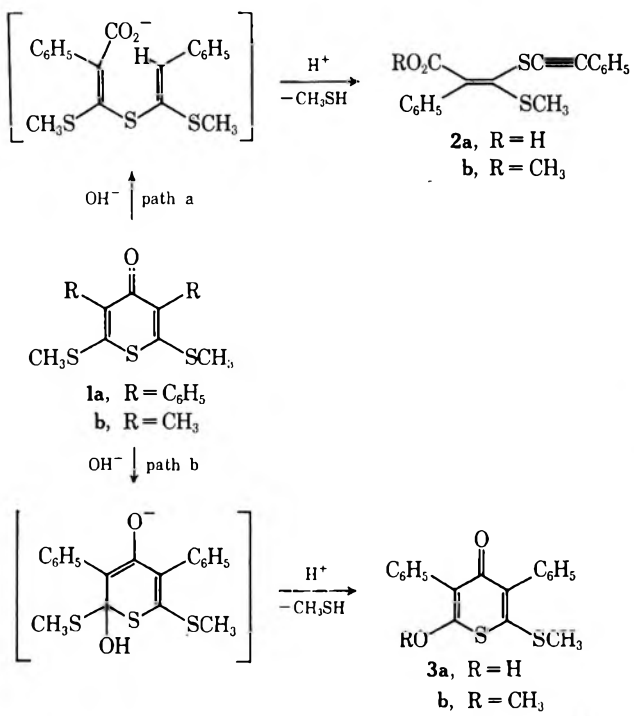
The reaction of 2,6-dimethylthio-3,5-diphenylthiapyrone (**1a**) with hydroxide ion has been reinvestigated. The major product of the reaction is shown to be the hydroxythiapyrone **3a**, which on treatment with diazomethane gives the isomeric enol ethers **3b** and **4b**. Spectral and chemical evidence used to support these conclusions are discussed.

In the course of our studies on the chemistry of thiapyrones, we have had occasion to reinvestigate the reaction of 2,6-dimethylthio-3,5-diphenylthiapyrone (**1a**) with hydroxide ion. Schönberg and Asker[2] described this reaction as leading to the complex thio ether **2a** *via* ring cleavage followed by the acid-catalyzed elimination of methanethiol. This sequence is indicated in path a. However, the only evidence offered in support of the assigned structure was an elemental analysis and demonstration of the acidic character of the product by its solubility properties and its reaction with diazomethane to form the "ester" **2b**.



2a, R = H
b, R = CH_3

1a, R = C_6H_5
b, R = CH_3

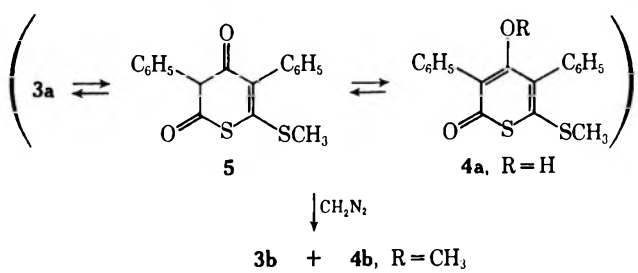
3a, R = H
b, R = CH_3

Our investigation of this reaction has revealed that the product is not **2a** but rather is the thiapyrone derivative **3a**, existing in solution in equilibrium with its tautomeric forms **4a** and **5**. When treated with diazomethane, this mixture produces the isomeric enol ethers **3b** and **4b**. The structural assignments of these products based on chemical and spectroscopic data are the subject of this report.

Results and Discussion

2-Methylthio-3,5-diphenyl-6-hydroxy-4-thiapyrone (**3a**) is produced in 38% yield by treatment of **1a** with alcoholic potassium hydroxide by the procedure described by Schönberg.[2] Path b, involving a Michael addition of hydroxide ion to **1a** followed by acidification and consequent elimination of methanethiol, suggests a possible route for its formation. This yellow crystalline material has the same melting point and other properties previously attributed to the incorrectly assigned structure **2a**.[2]

A key to the characterization of the acidic thiapyrone **3a** was its reaction with diazomethane. Since it seemed likely that **3a** should also exist as **4a**,[3] both tautomeric forms of the parent thia-2,4-pyrone **5**, methylation of



the tautomeric mixture was expected to produce the isomeric enol ethers **3b** and **4b**.[4] Careful chromatographic separation of the total reaction mixture afforded

(1) Paper II of this series: H. J. Teague and W. P. Tucker, *J. Org. Chem.*, **32**, 3144 (1967).

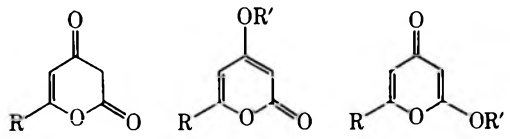
(2) A. Schönberg and W. Asker, *J. Chem. Soc.*, 604 (1946).

(3) The yellow hydrolysis product probably exists mainly as tautomer **4a** in both the solid state and in solution. Its visible absorption maximum (370 mμ) closely resembles that (380 mμ) of the α-thiapyrone ether **4b** (Table I).

(4) D. Herbert, W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 2427 (1959).

these isomers, one (**3b**) as white crystals, mp 156–158°, in 19% yield, and the other (**4b**) as a bright yellow solid, mp 151–153°, in 75% yield. This second product is the only one obtained when the work-up procedure described by Schönberg is employed, and is the product to which he assigned structure **2b**.[2]

Our assignment of structures to the products is based largely on a study of the ultraviolet–visible absorption spectra of these and similar compounds and on their nuclear magnetic resonance spectra. Djerassi and coworkers[4] have demonstrated that electronic absorption spectra can be used in distinguishing between the enol ethers produced by methylation of 2,4-pyrones **6** showing that the isomer with the longer wavelength absorption maximum represents the 2-pyrone derivative, **7b**.[5] Table I gives the ultraviolet–visible maxima of



6 **7a**, R′ = H; **b**, R′ = CH_3 **8a**, R′ = H; **b**, R′ = CH_3

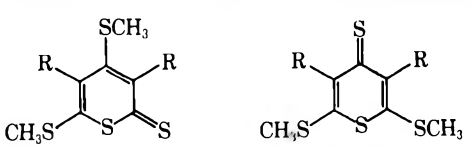
TABLE I

SPECTRAL PROPERTIES OF PYRONES AND THIAPYRONES

Compound	Uv–visible,[a,b] λ_{max}, mμ (log ε)	Pmr, δ,[c] 2(6)-CH_3	Pmr, δ,[c] 4-CH_3
1a	280 (4.23)	2.40	
1b	285 (3.69)	(2.46, 2.22)[d]	
3a	370 (3.87)	2.41	
3b	275 (4.07)	2.40 (3.82)	
4b	380 (3.96)	2.44	3.00
7b, R = CH_3	280 (3.80)[e]		
7b, R = C_6H_5	314 (4.13)[e]		
8b, R = CH_3	240 (4.13)[e]		
8b, R = C_6H_5	276 (4.29)[e]		
9a	498 (3.57)	(2.33, 2.52, 2.59, 2.72)[d]	
9b	500 (4.61)[f]	2.49	1.51
10a	405 (4.19)	(2.54, 2.62)[d]	
10b	408 (4.33)[f]	2.47	
11	480	2.52	2.98

[a] Ethanol solutions. [b] Longest wavelength absorption maxima. [c] Deuteriochloroform solvent with internal tetramethylsilane. [d] Rigorous assignment of these signals was not made. [e] These are only several of the examples given in ref 4. [f] Reference 7.

longest wavelength for a number of structurally similar pyrones and thiapyrones. Compounds **3b** and **4b**, as well as the previously reported thiothiapyrones **9b** and **10b**,[6] show the same correlation of structure with visible



9a, R = CH_3; **b**, R = C_6H_5 **10a**, R = CH_3; **b**, R = C_6H_5

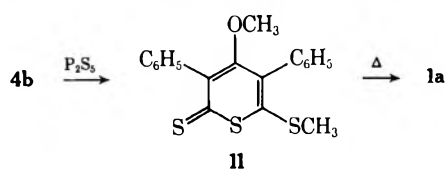
absorption as those studied by Djerassi.[4,7] Based on these data, the isomer with the longer wavelength absorption maximum is assigned structure **4b**. The similarity of the ultraviolet spectra of thiapyrones **1a** (λ_{max} 280 mμ), **1b** (λ_{max} 285 mμ), and **3b** (λ_{max} 275 mμ) reflects their structural resemblance.

It is interesting to note that the position of the absorption band of longest wavelength of the thiapyrones in Table I is not appreciably altered by substitution of methyl for phenyl in the 3 and 5 positions. (Compare for example, **1a** and **1b**, **9a** and **9b**, and **10a** and **10b**.) An examination of models indicates that the phenyl substituents cannot gain coplanarity with the heterocyclic ring and indeed must remain nearly perpendicular to it. Consequently, conjugation is minimized and its effect on the absorption spectra is very small.

The assignments of structures **3b** and **4b** are supported by the nmr data given in Table I. The presence of phenyl substituents in the 3 and 5 positions of the thiapyrones causes a marked difference in the chemical shifts of the protons of the adjacent S–CH_3 or O–CH_3 groups. The nmr spectra of a number of thiapyrones showed that the S–CH_3 group in the 2 position absorbs at *ca.* 2.4–2.5 ppm. However, when the S–CH_3 group is located in the 4 position and is flanked by phenyl substituents (as in **9b**) the methyl signal is shifted upfield by almost 1 ppm. A study of models shows that such an effect is to be expected in these compounds. Substituents in the **4** position are forced to remain above the plane of the phenyl rings where they are shielded because of the ring current effect.[8] In isomers **9a** and **10a**, which contain no phenyl substituents, little difference in the chemical shifts of the various methyl groups was observed.

The enol ethers produced by methylation of **3a** also exhibited a sharp difference in the chemical shifts of the O–CH_3 groups. In both isomers the absorption of O–CH_3 is lower than the corresponding S–CH_3 groups; however, in **4b**, the O–CH_3 group is shielded nearly 0.8 ppm more than that in **3b**. That this difference in O–CH_3 absorption is due to the ring currents of the phenyl substituents is borne out by an examination of models. The O–CH_3 group in the 4 position is shielded by the phenyl substituents to a greater degree than that in the 2 position. Thus, the nmr data support the assignments for **3b** and **4b** made on the basis of the ultraviolet–visible absorption data.

In an effort to distinguish chemically between **3b** and **4b**, **4b** was allowed to react with phosphorus pentasulfide in refluxing dioxane to produce the thiothiapyrone **11**. Heating **11** to the melting point (150°) resulted in



11

rearrangement to compound **1a**, the thiapyrone which was originally treated with hydroxide ion. Similar thion–thiol rearrangements have been previously studied.[7] This sequence of reactions confirms the structural assignments of the enol ethers. It seems unlikely that isomer **3b** could provide such a result since extensive rearrangement of atoms would be required.

(5) Infrared spectra can also be used to distinguish between these derivatives (ref 4) but are not sufficiently different for the thiapyrones to be useful in the present investigation.

(6) H. J. Teague and W. P. Tucker, *J. Org. Chem.*, **32**, 3140 (1967).

(7) Other examples illustrating this correlation and a theoretical discussion of it are found in a review by R. Mayer, W. Broy, and R. Zahradnik, *Advan. Heterocycl. Chem.* **8**, 247 (1967).

(8) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y. 1959, Chapter 7.

Experimental Section[9]

2,6-Dimethylthio-3,5-diphenyl-4-thiapyrone (**1a**).—The preparation of this compound is described in ref 6.

2,6-Dimethylthio-3,5-dimethyl-4-thiapyrone (**1b**).—This compound was prepared in 67% yield by the method of Apitzsch,[10] mp 122–123° (lit.[10] 123°).

2-Methylthio-3,5-diphenyl-6-hydroxy-4-thiapyrone (**3a**).—As described by Schönberg,[2] a solution containing 2.0 g of **1a** and 3.0 g of potassium hydroxide in 60 ml of ethanol was refluxed for 1 hr. The solution was acidified with dilute hydrochloric acid and allowed to stand for 1 day. The product which precipitated was collected and dried. Recrystallization from benzene afforded 0.35 g (38.5%) of **3a** as pale yellow crystals, mp 198–200° (lit.[2] 200°).

Anal. Calcd for $C_{18}H_{14}O_2S_2$: C, 66.23; H, 4.32; S, 19.65. Found: C, 66.44; H, 4.32; S, 19.40.

Methylation of 3a.—Compound **3a** (115.0 mg, 0.353 mmol) was added to a cold solution of diazomethane in ether and the solution maintained at 0° for 24 hr. Slow evolution of nitrogen was noted during this time. Removal of the solvent left a bright yellow residue. This residue contained two compounds and was separated by preparative thin layer chromatography (ptlc) (silica gel H with chloroform as developer). The faster moving band was yellow and yielded 90.2 mg (75%) of 2-methylthio-3,5-diphenyl-4-methoxy-2-thiapyrone (**4b**); recrystallization from heptane gave bright yellow crystals, mp 151–153° (lit.[2] 153°).

Anal. Calcd for $C_{19}H_{16}O_2S_2$: C, 67.01; H, 4.72; nuclidic mass, 340.0591. Found: C, 66.95; H, 4.61; nuclidic mass, 340.0597.

A second homogenous fraction, colorless, was removed from the silica gel and yielded 22.2 mg (18.5%) of 2-methylthio-3,5-diphenyl-6-methoxy-4-thiapyrone (**3b**); recrystallization from acetonitrile gave white needles, mp 156–158°.

Anal. Calcd for $C_{19}H_{16}O_2S_2$: C, 67.01; H, 4.72; nuclidic mass, 340.0591. Found: C, 66.86; H, 4.90; nuclidic mass, 340.0597.

2,6-Dimethylthio-3,5-dimethyl-4-thiothiapyrone (**10a**).—This compound was prepared from **1b** by the general procedure previously reported.[6] It was obtained in nearly quantitative yield; recrystallization from acetonitrile yielded bright red needles, mp 176–178°.

Anal. Calcd for $C_9H_{12}S_4$: C, 43.51; H, 4.87. Found: C, 43.25; H, 4.81.

2,4-Dimethylthio-3,5-dimethyl-6-thiothiapyrone (**9a**).—The preparation of this compound also followed the general procedure reported earlier.[6] In contrast to the thiapyrone derivatives with phenyl groups in the 3 and 5 positions, **9a** and **10a** possessed nearly identical R_f values in several solvent systems (chloroform, chloroform–hexane, benzene) making purification by ptlc more difficult. Purification was accomplished using silica gel H with ethyl acetate as developer. The 2-thiapyrone isomer (**9a**) moved slightly ahead of the 4 isomer (**10a**) and could be isolated in pure form by removing the top portion of the band (that portion which was homogenous in **9a**). Recrystallization from hexane yielded a red solid, mp 88–90°.

Anal. Calcd for $C_9H_{12}S_4$: C, 43.51; H, 4.87. Found: C, 43.40; H, 4.90.

2-Methylthio-4-methoxy-3,5-diphenyl-6-thiothiapyrone (**11**).—A solution of 100 mg of **4b** and 90 mg of phosphorus pentasulfide in 30 ml of *p*-dioxane was gently refluxed. The progress of the reaction was followed by tlc (silica gel H–chloroform) and the reaction was continued until all starting material disappeared or until more than one product appeared. The solvent was removed *in vacuo* and the reaction mixture leached with chloroform. This solution was concentrated and the products were separated by ptlc (aluminum oxide G–ethyl acetate) yielding approximately 60 mg (57%) of **11**. Recrystallization from methylene chloride–hexane gave red crystals, mp 150–152°.

Anal. Calcd for $C_{19}H_{16}OS_3$: C, 64.00; H, 4.50; S, 27.00; nuclidic mass, 356.0363. Found: C, 63.89; H, 4.39; S, 26.90; nuclidic mass, 356.0352.

Thermal Rearrangement of 11.—Under nitrogen, 50 mg of **11** was heated at 150° for 30 min; some decomposition was evidenced by a foul odor and by evolution of a colored gas. After this time analysis by tlc (silica gel H–chloroform) indicated that nearly all the red starting material had disappeared. The majority of the residue was an almost colorless material; small amounts of other compounds also appeared. The major component (80%) was isolated by ptlc (silica gel H–chloroform). Recrystallization from ethyl acetate yielded light yellow crystals, mp 163–165°, which proved to be **1a**. The identity of this product and **1a** was confirmed by tlc (many different solvents systems) and mixture melting point, 163–165°, and verified by identical ir spectra.

Registry No.—**1a**, 24097-29-8; **1b**, 24215-64-3; **3a**, 24097-30-1; **3b**, 24097-31-2; **4b**, 24097-32-3; **7b** (R = CH_3), 672-89-9; **7b** (R = C_6H_5, 4225-45-0; **8b**, (R = CH_3), 4225-42-7; **8b**, (R = C_6H_5), 4225-43-8; **9a**, 24097-37-8; **9b**, 24162-38-7; **10a**, 24162-39-8; **10b**, 14172-81-7; **11**, 24097-39-0; hydroxide ion, 14280-30-9.

Acknowledgment.—We wish to thank the National Science Foundation for a research grant (GP-7460) partially supporting these studies. We also thank Dr. David Rosenthal of the Research Triangle Center for Mass Spectrometry for the mass spectral analyses.

(9) Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Ultraviolet and visible spectra were measured in ethanol on a Beckman Model DK-2 spectrophotometer. The nmr spectra were determined in deuteriochloroform on a Varian HA-100 spectrometer and are reported in parts per million downfield from tetramethylsilane internal standard. Pertinent spectral data are included in Table I. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. High resolution mass spectral analyses were obtained on an Associated Electrical Industries MS-902 instrument. The absorbants used in thin layer chromatography separations were products of E. Merck (West Germany).

(10) H. Apitzsch, *Chem. Ber.*, **38**, 2888 (1905).

The Tricyclo[6.3.0.0^{4,8}]undecane System[1]

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Cyclodehydration of bicyclo[4.3.0]non-1(9)-ene-6-acetic acid (**4**) or a mixture of *syn*- and *anti*-tricyclo[4.3.1.0^{1,6}]-decane-10-carboxylic acid (**15**) with polyphosphoric acid yields tricyclo[6.3.0.0^{4,8}]undec-3-en-2-one (**6**) as the sole volatile product. The structure of **6** is established by conversion into methyl spiro[4.4]nonanecarboxylate (**9**). Some transformations of **6** are discussed.

Acid-catalyzed isomerizations have provided the only examples of the tricyclo[5.2.2.0^{1,6}]undecane skeleton, neoclovene (**1**)[2] and ketone **2**.[3] One synthetic approach to this carbon skeleton involves recognition of the objective as an ethano-bridged hydrindan, **3**. Here we report the discovery of a rearrangement in the cyclodehydration of acid **4**, which led to the new tricyclo[6.3.0.0^{4,8}]undecenone (**6**), rather than the desired tricyclo[5.2.0.0^{1,6}]undecenone (**5**).

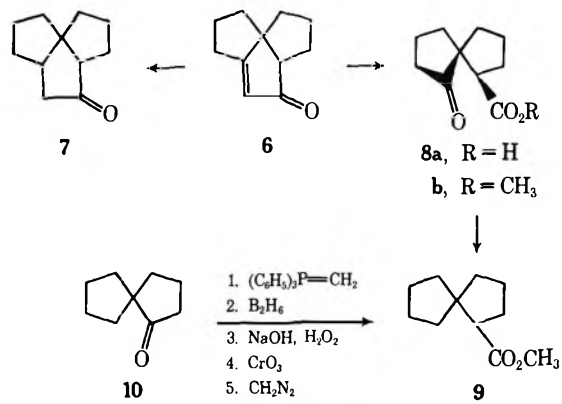
1 **2** **3**

Cyclodehydration of acid **4** seemed a reasonable candidate for the preparation of ketone **5**. In the event, treatment of **4** with polyphosphoric acid (PPA) provided a single unsaturated ketone in 31% yield. The new ketone was assigned structure **6** after consideration of the spectral data,[4] which show the presence of a cyclopentenone bearing a single vinyl hydrogen, and that at the α position.

4 **5** **6**

Subsequent chemical degradation confirmed our assignment. Catalytic hydrogenation of **6** yields a cyclopentanone (**7**), and oxidation (periodate–permanganate) yields a C_{10} keto acid (**8a**) in which the ketone function is a cyclopentanone. Wolff–Kishner reduction of the keto acid followed by esterification provides the new ester **9**,[5] which was identified by comparison with an authentic sample prepared from ketone **10**,[6] as is outlined in Scheme I. The conversion of the new ketone **6** into ester **9** by the sequence described defines the positions of 10 of the 11 carbons unambiguously. To reconstruct mentally the unknown ketone from ester **9** we need only consider that one trigonal carbon

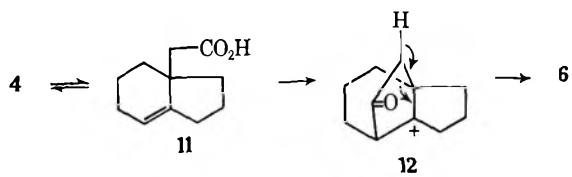
SCHEME I



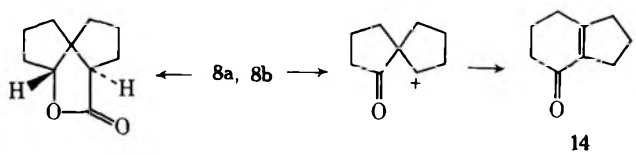
(corresponding to the trigonal C_α removed by oxidation) must be attached to the spiran through a carbon–carbon double bond as well as to the carboxyl at C_1, such that a normal α,β-unsaturated ketone results. Only at C_2 and C_6 is this possible.[7] The former position is eliminated by the evidence already presented; therefore, structure **6** is firmly established.

Ketone **6** evidently arises by isomerization of acid **4** to the more stable **11**, which then undergoes intramolecular acylation followed by a Wagner–Meerwein shift and proton elimination as is depicted in Scheme II.

SCHEME II



Keto ester **8b** was further characterized by reduction with sodium borohydride to yield lactone **13**; oxidative decarboxylation of **8a** with lead tetraacetate yielded the rearranged ketone **14**. The latter may be considered to arise *via* an acyl shift in the carbonium ion formed by the decarboxylation of **8a**.[8]



(1) We thank the National Science Foundation for generous support of this research.

(2) (a) W. Parker, R. A. Raphael, and J. S. Roberts, *Tetrahedron Lett.*, 2313 (1965); (b) T. F. W. McKillop, J. Martin, W. Parker, and J. S. Roberts, *Chem. Commun.*, 162 (1967).

(3) R. L. Cargill, M. E. Beckham, and J. R. Damewood, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, No. P179.

(4) See Experimental Section for spectral data.

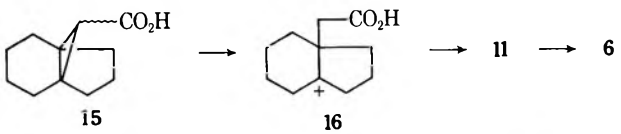
(5) The acid corresponding to **9** was reported as an uncharacterized oil: N. N. Chatterjee, *J. Indian Chem. Soc.* **14**, 259 (1937).

(6) R. K. Hill and R. T. Conley, *J. Amer. Chem. Soc.*, **82**, 645 (1960).

(7) Bicyclic olefins having double bonds at the bridgeheads have been prepared, but the bicycloheptenes and bicyclooctenes remain fugitive. See J. A. Marshall and H. Faubl, *ibid.*, **89**, 5965 (1967); J. R. Wiseman, *ibid.*, **89**, 5966 (1967); J. R. Wiseman, H. F. Chan, and C. J. Ahola, *ibid.*, **91**, 2812 (1960).

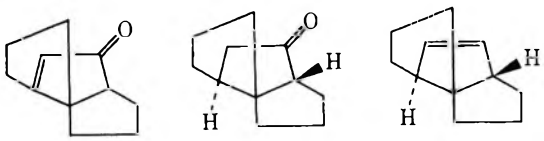
(8) (a) E. J. Corey and J. Casanova, *ibid.*, **85**, 165 (1963); (b) G. Buchi, R. E. Erickson, and N. Wakabayashi, *ibid.*, **83**, 927 (1961).

Our interest in the chemistry of the tricyclic system represented by ketone **6** led us to develop a route to that enone which is somewhat more efficient than is the cyclodehydration of **4** or **11**. Acids **4** and **11** may be prepared by the method developed by Burgstahler,[9] an elegant but somewhat time-consuming sequence. Since isomerization of **4** to **11** must proceed *via* ion **16**, we considered that the cyclopropyl acids **15**,[10] which are more readily available than are acids **4** or **11**, would undergo acid-catalyzed ring opening to yield acid **11** and subsequent ring closure to give ketone **6**. Indeed, ketone **6** was obtained in 60% yield when acids **15** were heated in PPA at 100° for 45 min. The cyclodehydration of acids **15** provides another example of the utilization of a cyclopropane ring to introduce an angular substituent on a polycyclic nucleus.[11]



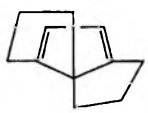
15 16

Saturated ketone **7** is readily converted into the monoolefin **17** by the method of Shapiro.[12] The nmr spectrum of olefin **17** (see Experimental Section), which strongly indicates C_2 molecular symmetry in that olefin, provides support for the stereochemical assignments shown in formulas **7** and **17**.



6 7 17

The transformations of ketone **6** described here provide paths to 1,6-disubstituted spiro[4.4]nonanes as well as the basis for further exploration of the chemistry of the tricyclo[6.3.0.0^{4,8}]undecane system, including the synthesis of the chiral diene **18**. We shall report further on our efforts to prepare diene **18**. In addition, other variations of our previously outlined approach to the tricyclo[5.2.0.0^{1,6}]undecane system (see formula **3**) will be described in subsequent papers.



18

Experimental Section[13]

Bicyclo[4.3.0]non-1(9)-ene-6-acetic Acid (4).—The corresponding aldehyde was prepared through an angular alkylaton adapted from the procedure of Burgstahler and Nordin.[9] The overall yield of bicyclo[4.3.0]non-1(9)-ene-6-acetaldehyde from bicyclo[4.3.0]non-1(6)-en-7-one was 30%: ir (CCl_4) 3020, 2700, and 1720 cm^{-1}; nmr (CCl_4) δ 9.50 (t, 1, J = 2.5 Hz, $-CH_2-CHO$), 5.2 (m, 1, $-CH=C$).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.39; H, 9.89.

To a solution of 3.43 g of the above aldehyde in 300 ml of acetone and 100 ml of water was added 12 ml of stock chromic anhydride solution (prepared from 27 g of chromic anhydride and 23 ml of sulfuric acid diluted to 100 ml with water) and the resulting mixture was stirred at 25° for 7 hr. Aqueous sodium carbonate solution was added and the mixture was washed twice with pentane. The aqueous portion was acidified with hydrochloric acid, saturated with sodium chloride, and extracted three times with ether. The combined ethereal extracts were dried and concentrated to yield 3.16 g of crude bicyclo[4.3.0]non-1(9)-ene-6-acetic acid (**4**): ir (neat) 3600–2600 and 1710 cm^{-1}. Esterification with diazomethane gave the methyl ester (single compound by glpc): ir (neat) 3030 and 1735 cm^{-1}; nmr (CCl_4) δ 5.14 (m, 1, $-CH=C$) and 3.53 (s, 3, $-CO_2CH_3$).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.35. Found: C, 74.22; H, 9.23.

Periodate–Permanganate Cleavage of Acid 4.—To a solution of 1.44 g of sodium periodate, 0.0179 g of potassium permanganate, 0.350 g of potassium carbonate, and 340 ml of water was added 0.152 g of **4** in 1 ml of ether. The mixture was stirred at 25° for 2 days, 0.1 g of sodium hydroxide was added, and the alkaline solution was washed twice with pentane. The aqueous solution was acidified with sulfuric acid, saturated with sodium chloride, and extracted three times with ether. The ethereal solution was dried and concentrated to afford 0.258 g of crude 1-(carboxymethyl)-2-oxocyclohexanepropionic acid: ir (CCl_4) 3600–2500 and 1715 cm^{-1}. Esterification with diazomethane gave the keto diester (purity greater than 90% by glpc): ir (CCl_4) 1735 and 1710 cm^{-1}; nmr (CCl_4) δ 3.55 (s, 6, $-CO_2CH_3$).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.91; H, 8.14.

Tricyclo[6.3.0.0^{4,8}]undec-3-en-2-one (6).—A mixture of 2.78 g of crude **4** and 53 g of polyphosphoric acid was heated at 100° for 2 hr with occasional stirring. The reaction mixture was quenched with ice and extracted three times with pentane. The organic portion was washed with sodium bicarbonate and saturated sodium chloride solutions, dried, concentrated, and chromatographed over alumina with 25% ether in pentane. The eluate was concentrated and distilled to give 0.784 g (31%) of tricyclo[6.3.0.0^{4,8}]undec-3-en-2-one (**6**): bp 80° (0.5 Torr); ir (CCl_4) 1710 and 1635 cm^{-1}; nmr (CCl_4) δ 5.61 (br s, 1, $-CH=C$); uv max (95% C_2H_5OH) 235 mμ (ϵ 11,300).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.49; H, 8.59.

Tricyclo[6.3.0.0^{4,8}]undecan-2-one (7).—Catalytic hydrogenation (5% palladium on charcoal) of 1.10 g of **6** yielded 0.99 g of distilled tricyclo[6.3.0.0^{4,8}]undecan-2-one (**7**): bp 61° (0.3 Torr); ir (CCl_4) 1735 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.54; H, 9.67.

Periodate–Permanganate Cleavage of 6.—To a solution of 3.80 g of sodium periodate, 0.050 g of potassium permanganate, 0.913 g of potassium carbonate, and 890 ml of water was added 0.353 g of **6** in 0.5 ml of ether. After 2.5 days the reaction was worked up as previously described. The crude product was crystallized from *n*-hexane (charcoal), giving 0.208 g of *cis*-6-oxospiro[4.4]nonanecarboxylic acid (**8a**), mp 70–72°. A pure sample was obtained after two recrystallizations from *n*-hexane: mp 71–71.5°; ir (CCl_4) 3600–2400, 1740, and 1715 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.95; H, 7.72.

Esterification with diazomethane gave the corresponding methyl ester **8b**: ir (CCl_4) 1740 and 1735 cm^{-1}; nmr (CCl_4) δ 3.52 (s, 3).

Anal. Calcd for $C_{11}H_{15}O_3$: C, 67.32; H, 8.22. Found: C, 67.46; H, 8.47.

(9) A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, **83**, 198 (1961).

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

(11) For some examples see (a) ref 10; (b) J. J. Sims, *ibid.*, **32**, 1751 (1967); (c) J. J. Sims, *J. Amer. Chem. Soc.*, **87**, 3511 (1965); (d) T. Hanafusa, L. Birladeanu, and S. Winstein, *ibid.*, **87**, 3510 (1965); (e) D. J. Beames and L. N. Mander, *Chem. Commun.*, 498 (1969); (f) R. D. Stiptanovic and R. B. Turner, *J. Org. Chem.*, **33**, 3261 (1968), and J. J. Sims and V. K. Honwad, *ibid.*, **34**, 496 (1969).

(12) R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967).

(13) All boiling points and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, West Germany, or by Gailbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined in carbon tetrachloride unless otherwise stated, using either a Perkin-Elmer Model 337 or 257 grating spectrophotometer. All nmr spectra were determined in carbon tetrachloride containing 5% tetramethylsilane as an internal standard using a Varian A-60 nmr spectrometer. Analytical gas–liquid partition chromatograms were determined using a Varian Aerograph Model 1200 chromatograph, and preparative glpc separations were conducted using a Varian Aerograph 90-P-3 chromatograph. Liquid samples were purified for combustion analysis by glpc followed by vacuum distillation onto a cold finger.

Modified Wolff–Kishner Reduction of Keto Acid 8a.—To a solution of 0.21 g of potassium hydroxide, 0.15 ml of hydrazine hydrate, and 1.5 ml of diethylene glycol was added 0.20 g of **8a**. The solution was heated under reflux for 1 hr, and then the temperature was raised to 190–200°. After an additional 2 hr the volatile material had been removed and the reaction was cooled, dilute hydrochloric acid was added, and the mixture was extracted with ether. The ethereal extract was dried and concentrated to give 0.18 g of crude spiro[4.4]nonanecarboxylic acid. Esterification with diazomethane gave methyl spiro[4.4]-nonanecarboxylate (**9**) (see below).

Methylenespiro[4.4]nonane.—The conversion of 11.06 g of spiro[4.4]nonanone[14] (**10**) into the methylene analog was carried out with methylenetriphenylphosphorane in dimethyl sulfoxide according to the procedure of Corey.[15] A yield of 8.02 g of methylenespiro[4.4]nonane was obtained: bp 78° (25 Torr); ir (CCl_4) 3069, 1655, and 880 cm^{-1}; nmr (CCl_4) δ 4.67 (s, 2, $>C{=}CH_2$), 2.28 (m, 2), and 1.56 (s, 12).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.38; H, 11.61.

Hydroxymethylspiro[4.4]nonane.—To a solution of 4.0 g of methylenespiro[4.4]nonane and 0.42 g of sodium borohydride in 25 ml of diglyme maintained at 0° was added dropwise with stirring 1.85 ml of boron trifluoride etherate. The reaction mixture was warmed to 25° and stirring was continued for 1 hr. Then 3.1 ml of 3 *N* sodium hydroxide was added followed by 3.1 ml of 30% hydrogen peroxide and the solution was stirred for 30 min. The resulting mixture was poured into 100 ml of water and was extracted with ether. The organic portion was washed twice with ice water, dried, and concentrated to give 5.47 g of crude hydroxymethylspiro[4.4]nonane: bp 60° (0.5 Torr); ir (CCl_4) 3610 and 3500–3200 cm^{-1}; nmr (CCl_4) δ 3.40 (m, 2 CH_2OH) and 3.35 (s, 1, –OH).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.74; H, 11.92.

Methyl Spiro[4.4]nonanecarboxylate (9).—To an ice-cooled solution of 1.46 g of hydroxymethylspiro[4.4]nonane in 9.3 ml of aqueous sulfuric–acetic acid (prepared from 5 ml of sulfuric acid and 10 ml of water diluted to 50 ml with acetic acid) was added at once 8.2 ml of chromic anhydride solution (prepared from 12.5 g of chromic anhydride in 12.5 ml of water diluted to 50 ml with acetic acid). The mixture was stirred at 25° for 4 hr and and then heated to 100° for 0.5 hr. Approximately 50 ml of water was added and the mixture was extracted three times with ether. The ethereal portion was extracted three times with 1 *N* sodium hydroxide, and the alkaline solution was washed with hexane and then acidified with sulfuric acid. The resulting emulsion was extracted twice with pentane and the organic portion was dried and concentrated to yield 0.725 g (40% from **10**) of spiro[4.4]nonanecarboxylic acid. Esterification with diazomethane gave methyl spiro[4.4]nonancarboxylate (**9**) (single compound by glpc): ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) δ 3.52 (s, 3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.67; H, 9.90.

(14) R. K. Hill and R. T. Conley, *J. Amer. Chem. Soc.*, **82**, 645 (1960).

(15) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

Lithium aluminum hydride reduction of **9** regenerated hydroxymethylspiro[4.4]nonane.

Oxidative Decarboxylation of Keto Acid 8a.—A solution of 0.100 g of **8a**, 0.07 ml of pyridine, and 0.211 g of lead tetraacetate in 1.5 ml of benzene was stirred with gentle refluxing under a nitrogen atmosphere for 7 hr. The reaction mixture was eluted from alumina with ether and the eluate was washed twice with 1 *N* sodium hydroxide, twice with brine, twice with 1 *N* hydrochloric acid, and twice again with brine. Removal of solvent gave exclusively the known bicyclo[4.3.0]non-1(6)-en-2-one (**14**).[16]

Cyclodehydration of Acids 15.[10]—A mixture of 4.60 g of acids **15** and 90 g of polyphosphoric acid was stirred at 100° for 45 min. The reaction was worked up as previously described, yielding 2.41 g of distilled tricyclo[6.3.0.0^{4,8}]undec-3-en-2-one (**6**).

Tricyclo[6.6.0.0^{4,8}]undec-2-ene (17).—A solution of 0.627 g of tricyclo[6.3.0.0^{4,8}]undecan-2-one (**7**), 0.760 g of tosylhydrazide, and 0.03 ml of hydrochloric acid in 3 ml of ethanol was refluxed for 1 hr and then allowed to stand at 25° overnight. Removal of solvent gave crude tosylhydrazone, which was dissolved in 25 ml of ether and treated with 7.6 ml of 2.0 *M* *n*-butyllithium. Gas evolution was evident; after 10 min 25 ml of water was added and the mixture was extracted twice with pentane. The dried organic portion was concentrated and the residue was distilled (0.5 Torr, bath temperature 90°) to give 0.232 g (41%) of tricyclo[6.3.0.0^{4,8}]undec-2-ene (**17**): ir (CCl_4) 3025 cm^{-1}; nmr (CCl_4) δ 5.31 (s, 2, HC=CH), 2.59 (m, 2), and 1.51 (br s, 12).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.05; H, 11.00.

***cis,cis*-6-Hydroxyspiro[4.4]nonane-1-carboxylic Acid Lactone (13).**—To a stirred solution of 0.22 g of keto ester **8b** in 3.2 ml of methanol at 0° was added 25 mg of sodium borohydride. After 30 min 3 ml of dilute hydrochloric acid was added and the mixture was extracted with ether. The ethereal extract was concentrated to give crude *cis,cis*-6-hydroxyspiro[4.4]nonane-1-carboxylic acid lactone (**13**) containing an uncharacterized ester impurity. The crude product was refluxed for 5 hr in 10% aqueous sodium hydroxide. The mixture was neutralized with dilute hydrochloric acid and extracted with ether. The organic layer was washed twice with sodium bicarbonate, dried, concentrated, and collected by glpc (DEGS) to give 0.079 g of *cis,cis*-hydroxyspiro[4.4]nonane-1-carboxylic acid lactone (**13**): ir (CCl_4) 1775 cm^{-1}; nmr (CCl_4) δ 4.27 (m, 1, HCO).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.47; H, 8.57.

Registry No.—Bicyclo[4.3.0]non-1(9)-ene-6-acetaldehyde, 24097-40-3; 1-(carboxymethyl)-2-oxocyclohexanepropionic acid dimethyl ester, 24097-42-5; methylenespiro[4.4]nonane, 19144-06-0; hydroxymethylspiro-[4.4]nonane, 24097-45-8; methyl ester of **4**, 24097-41-4; **6**, 24097-43-6; **7**, 24215-67-6; **8a**, 24097-75-4; **8b**, 24097-76-5; **9**, 24097-46-9; **13**, 24097-77-6; **17**, 24097-78-7.

(16) R. K. Hill and R. T. Conley, *Chem. Ind.* (London), 1314 (1956).

Novel Dimeric Products from 10-Methyleneanthrone[1]

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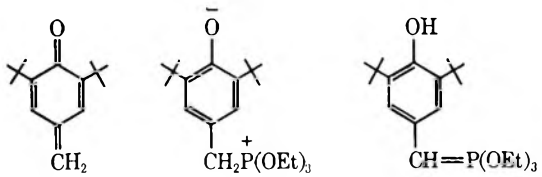
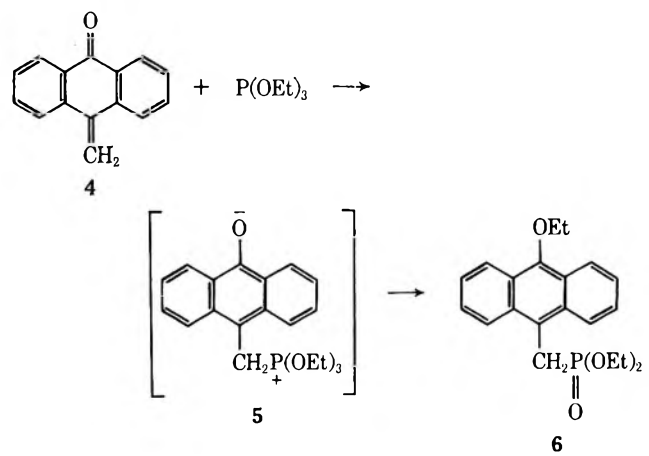
1,2-Dihydro-7-ethoxy-3H-benz[*de*]anthracene-3-spiro-10′-anthrone (**7a**) is shown to be a major by-product (14% yield) of the reaction of 10-methyleneanthrone (**4**) with triethyl phosphite (1 molar equiv) at 95°. Mechanistic studies suggest that **7a** is formed *via* a path involving Diels–Alder dimerization of **4**, abstraction of a proton from the dimer, and alkylation of the resulting anion with a phosphonium betaine generated *in situ*. In contrast to a literature report, oxidation of 9-methoxy-10-methylanthracene (**13**) with anhydrous cupric chloride (2 molar equiv) in refluxing benzene or carbon tetrachloride gives 1,2-dihydro-7-methoxy-3H-benz[*de*]anthracene-3-spiro-10′-anthrone (**7b**) as the major product (*ca.* 60–70% yield). Spiroanthrones **7a** and **7b** can also be prepared in *ca.* 50% yield by reaction of **4** with an excess of ethyl iodide or methyl iodide in hot methanolic sodium methoxide. Oxidation of **4** with molecular oxygen occurs readily in benzene at 24–25° and gives anthraquinone (**17**), spiro[anthracene-9(10H),2′-oxiran]-10-one (**18**), and other products. The dimerization tendency and autoxidative susceptibility of **4** thus appear to be greater than has been realized heretofore.

The reaction of triethyl phosphite with quinone methide **1** was described in the previous paper of this



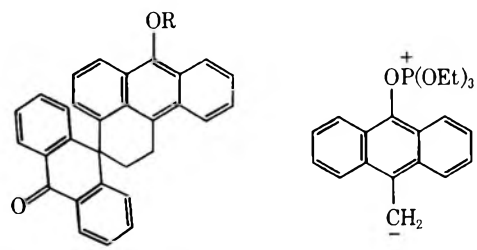
series.[1b] Phosphite-catalyzed dimerization of **1** was shown to be the major reaction path, and betaine **2** and ylide **3** were implicated as key intermediates.[1b] During the course of this work,[1b] the reaction of triethyl phosphite with another *p*-quinone methide, 10-methyleneanthrone (**4**), was described in two independent reports.[2] In both cases the only identified product was phosphonate **6** (yield, 61[2a] or 18%[2b]),[3] a substance whose precursor was evidently betaine **5**.[2a] A product



analogous to **6** had not been obtained from betaine **2**;[1b] however, this result did not seem particularly surprising, since it appeared readily rationalizable in terms of steric factors. Of greater significance was the finding that the reaction of triethyl phosphite with **4** also gave a by-product, mp 218–220°, *that did not contain phosphorus*.[2b] Suspecting that this by-product might be an impure dimer resulting from phosphite-catalyzed condensation of the quinone methide, we felt that a brief reinvestigation of this reaction would be of special interest in connection with our related studies on **1**. The present paper is concerned with the identification and mechanism of formation of a dimeric species derived from **4** and triethyl phosphite and with the production of analogous dimers in certain related reactions.

Results and Discussion

Reaction of 10-Methyleneanthrone (4) with Triethyl Phosphite.—This reaction was carried out under conditions very similar to those employed by Arbuzov, *et al.*[2b] Work-up[2b] afforded a yellow solid that did not contain phosphorus and was conclusively identified as 1,2-dihydro-7-ethoxy-3H-benz[*de*]anthracene-3-spiro-10′-anthrone (**7a**, 14% yield) by various spectrometric measurements (Experimental Section). The



pure spiroanthrone melts at 236–237.5°, and its elemental composition is similar to that of the Russian workers' product;[2b] whether the two substances are, in fact, the same cannot be ascertained at present.

A plausible mechanism for the formation of **7a** is shown in Scheme I. Reaction 1 is consistent with the well-established behavior of **4** as a Diels–Alder diene.[4] Additions of **4** to other diene systems have apparently not been observed previously, although the ability of quinone methide **1** to function as a dienophile has been adequately demonstrated.[5] It might be supposed that reaction **1** is actually *catalyzed* by triethyl phosphite in a process involving three steps: formation of betaine **8** from the phosphite and **4**, addition of the carbanion

(1) (a) Paper VI of a series on oxidation inhibitors. (b) Paper V: W. H. Starnes, Jr., J. A. Myers, and J. J. Lauff, *J. Org. Chem.*, **34**, 3404 (1969). (c) Presented at the 25th Southwest Regional Meeting of the American Chemical Society, Tulsa, Okla., Dec 4–6, 1969.

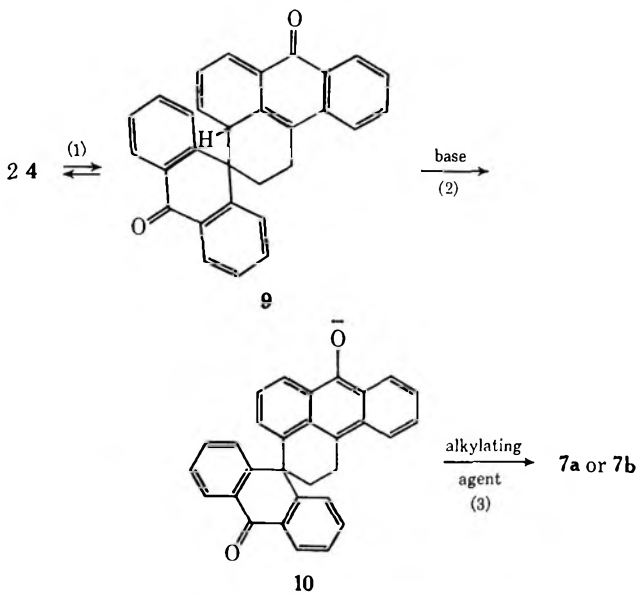
(2) (a) A. N. Al-Khafaji, Ph.D. Dissertation, University of Texas, Austin, Texas, 1966; (b) B. A. Arbuzov, V. M. Zoroastrova, and N. D. Ibragimova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 687 (1967).

(3) These yields are recalculated values based on the actual numerical data of ref 2a and b.

(4) See, *inter alia*, (a) J. A. Norton, *Chem. Rev.*, **31**, 319 (1942), and references therein; (b) I. T. Millar and K. E. Richards, *J. Chem. Soc., C*, 855 (1967).

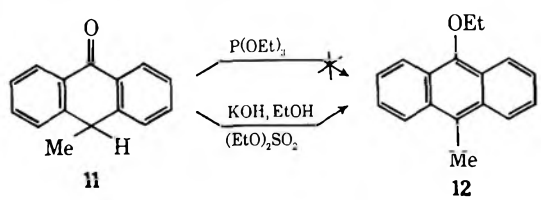
(5) J. D. McClure, *J. Org. Chem.*, **27**, 2365 (1962).

SCHEME I



moiety of **8** to the methylene group of a second quinone methide molecule, and internal cyclization of the newly formed betaine to form **9** and regenerate the phosphite. Although this sequence cannot be rigorously excluded, it seems rather unlikely in view of the phosphite's apparent preference for addition to the methylene group of **4** (as demonstrated by the isolation of **6**).[2] Also applicable here are some of our previous arguments against the addition of triethyl phosphite to the carbonyl group of **1**.[1b] Furthermore, postulation of a catalyzed dimerization of **4** actually seems unnecessary, since spontaneous dimerization apparently does occur in a closely related reaction. First described by Al-Khafaji,[2a] the reaction in question ensues when **4** and an alkyl iodide are heated together in methanolic sodium methoxide. If ethyl iodide is employed, the product is spiroanthrone **7a**.[2a] This result is clearly best accounted for by the mechanism of Scheme I (alkylating agent = EtI),[2a] with reaction 1 occurring in a spontaneous manner. In the present work Al-Khafaji's preparation of **7a** was repeated and found to give a product identical with that obtained from **4** and triethyl phosphite. Moreover, we also found that **4** was not converted to **9** (or other dimeric products) by refluxing in methanol alone. These observations indicate that reaction 1 is reversible and that the equilibrium lies far to the left under the conditions employed.

In the reaction of **4** with triethyl phosphite, conversion of **9** to **7a** might be considered to involve abstraction of the labile proton of **9** by the phosphite (reaction 2), followed by reaction of the protonated phosphite with anion **10** to form diethyl phosphite and **7a** (reaction 3). The feasibility of this sequence was tested by examining the behavior of triethyl phosphite toward two model compounds, 10-methylanthrone (**11**) and phenol, under conditions identical with those

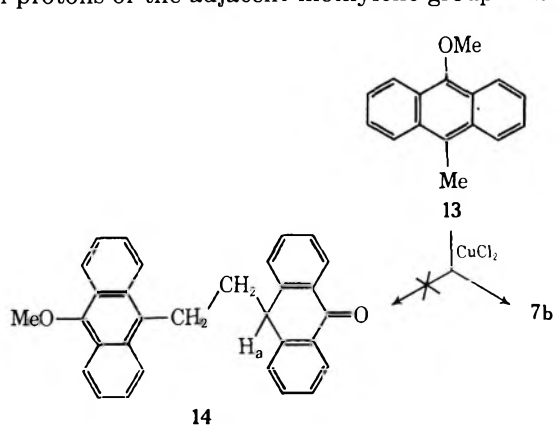


11 12

employed for reaction of the phosphite with **4**. An nmr spectral comparison *vs.* authentic 9-ethoxy-10-methylanthracene (**12**, prepared by alkylation of **11** with diethyl sulfate in ethanolic potassium hydroxide) showed that this ether was not formed in the reaction with **11**. Furthermore, no phenetole was formed in the reaction with phenol, a result consistent with the phosphite's failure to alkylate hydroquinone under more vigorous conditions.[6] In view of these facts, an Arbuzov-type reaction between anion **10** and protonated triethyl phosphite seems highly unlikely. On the other hand, alkylation of **10** by betaine **5** (or this betaine's conjugate acid) is a very reasonable possibility. The apparent conversion of **5** to **6** constitutes a very close analogy for such a reaction, and another analogy is provided by the well-documented formation of phenetole from phenol and various alkyltriethoxyphosphonium betaines.[7]

In summary, it appears that the mechanism of Scheme I adequately accounts for spiroanthrone formation in the reactions of **4** discussed above. In both cases the Diels–Alder dimerization of **4** (reaction 1) probably occurs spontaneously and reversibly. In the reaction with triethyl phosphite, either betaine **5** or the phosphite itself could serve as the requisite base (reaction 2), and in this system anion **10** is probably alkylated (reaction 3) by betaine **5** and/or this betaine's conjugate acid. Reaction 2 might also be significantly reversible under certain conditions; however, protonation of **10** on C-3a (the labile proton's original point of attachment) seems much less likely than protonation of **10** on anionic oxygen or on C-11b.

Spiroanthrone 7b from Oxidation of 9-Methoxy-10-methylanthracene (13) with Anhydrous Cupric Chloride.—While the present investigation was in progress, Nonhebel and Russell[8] reported the formation of a novel dimeric product in oxidations of anthracene **13** with cupric chloride or cupric bromide. Obtained in 65–77% yield, the dimer was considered to be **14**, even though its nmr spectrum failed to show coupling of H_a with protons of the adjacent methylene group.[8] Since



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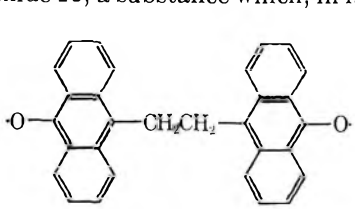
the spectral properties reported for this dimer were quite similar to those expected for spiroanthrone **7b**, a reinvestigation of the structure of **14** was of obvious interest within the context of the present work. The results of Nonhebel and Russell could not be checked directly, since these workers did not report the melting

(6) V. A. Ginsburg and A. Y. Yakubovich, *J. Gen. Chem. USSR*, **30**, 3944 (1960).
(7) R. G. Harvey, *Tetrahedron*, **22**, 2561 (1966).
(8) D. C. Nonhebel and J. A. Russell, *Chem. Ind.* (London), 1841 (1968).

point of their product or give details for its preparation. However, Nonhebel had previously described a general procedure for oxidation of aromatics with cupric halides.[9] Using this procedure, we oxidized **13** with anhydrous cupric chloride in benzene and obtained a product (approximate yield, 60–70%) that was conclusively identified as spiroanthrone **7b** by appropriate spectral measurements (Experimental Section). An oxidation in carbon tetrachloride gave a similar result, and no evidence could be obtained for the presence of **14** in either of the product mixtures. Compound **7b** prepared in this way had mp 221–222°, whereas mp 237–239° was observed for a reference sample prepared from **4** by the method of Al-Khafaji.[2a] However, the ir spectra of the two samples were identical in every respect, and their nmr spectra were also superimposable. The materials were therefore considered to be different crystalline modifications of **7b**, a conclusion that was further substantiated by conversion of the high-melting form to the low-melting form upon recrystallization, using the low-melting form for seeding. Structures **7b** and **14** have similar elemental compositions, and the spectral properties reported for **14** differ from those of **7b** in only one significant respect: the integrated intensities for the aromatic and methoxyl protons, as determined by nmr.[8] It therefore appears that the compound thought[8] to be **14** may actually have been **7b**, although this conclusion cannot be drawn with certainty in the absence of additional information relating to the results of Nonhebel and Russell.[8]

The mechanism for conversion of **13** to **7b** is obscure. A possible path (not necessarily the preferred one) would involve oxidative cyclization of **14**.

Oxidation of 10-Methyleneanthrone (4) with Molecular Oxygen.—The spontaneous dimerization–disproportionation of quinone methide **1** proceeds *via* a bisphenoxy radical intermediate.[10] This observation suggests the possible intermediacy of an analogous diradical (**15**) in the spontaneous conversion of **4** to **9**. Reaction of **15** with molecular oxygen might be expected to yield peroxide **16**, a substance which, in fact, has been



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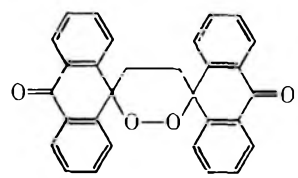

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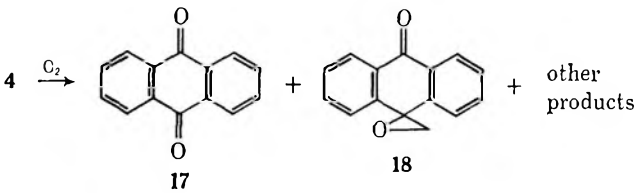
reported to result from the photooxidation of **4**.[11] In view of these considerations, it appeared that an oxygen trapping experiment might provide evidence for the spontaneous (nonphotochemical) formation of **15**. Accordingly, a suspension of **4** in benzene was stirred for several days in the dark at room temperature under an atmosphere of pure oxygen. A considerable amount of oxygen (0.45 mol/mol of **4**) was absorbed, and the product mixture was found to contain appreciable quantities of anthraquinone (**17**) and spiro[anthracene-9(10H),2′-oxiran]-10-one (**18**). The presence



17 **18**

of its characteristic odor indicated that formaldehyde was also a product, and the formation of **16** was suggested by a positive peroxide test and the presence of a sharp nmr singlet whose chemical shift (δ 2.14 ppm) fell within the range expected for resonance by the methylene protons of the cyclic peroxide. On the assumption that **16** was actually present, the yields of **16**, **17**, **18**, and recovered **4** were estimated from nmr measurements as 17, 34, 35, and 23%, respectively. Although these results cannot be regarded as conclusive evidence for the spontaneous formation of **15**, they do demonstrate the occurrence of an interesting autoxidation[12] which was apparently not detected by previous workers.

10-Methyleneanthrone (**4**) has been frequently referred to in the literature as being the only extant example of a stable (isolable) quinone methide containing an unsubstituted *exo*-methylene moiety.[13] It now appears that the Diels–Alder dimerization of **4** is actually quite facile (though highly reversible), and that this quinone methide is more susceptible to autoxidation than has been realized heretofore.[14]

Experimental Section[15]

Materials.—Triethyl phosphite was distilled *in vacuo* under nitrogen and stored under nitrogen at −15°; it contained no impurities detectable by nmr or vpc analysis. Benzene was dried over sodium ribbon. Anhydrous cupric chloride was prepared by heating the dihydrate under vacuum at 110°. The other chemicals used were either highly purified articles of commerce or materials prepared by standard literature procedures, as indicated below. Purities were verified by spectral measurements, vpc analyses, and the determination of appropriate physical constants.

(9) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963).

(10) R. H. Bauer and G. M. Coppinger, *Tetrahedron*, **19**, 1201 (1963); N. P. Neureiter, *J. Org. Chem.*, **28**, 3486 (1963); B. R. Loy, *ibid.*, **31**, 2386 (1966).

(11) A. Mustafa and A. M. Islam, *J. Chem. Soc.*, S81 (1949).

(12) Noteworthy features of this oxidation are the relatively high yield of **18** and the apparent absence of 10-methyleneanthrone polyperoxide from the products. Possible routes to the autoxidation products of **4** are suggested by Mayo's work on the autoxidation of styrene [F. R. Mayo, *J. Amer. Chem. Soc.*, **80**, 2465 (1958), and references therein], but firm mechanistic conclusions are obviously unwarranted in the absence of additional information.

(13) See, *inter alia*, ref 2a and 4b, and A. B. Turner, *Quart. Rev.* (London), **18**, 347 (1964).

(14) For an earlier comment on the autoxidative stability of **4**, see P. L. Julian, W. Cole, and T. F. Wood, *J. Amer. Chem. Soc.*, **57**, 2508 (1935).

(15) Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Drierite was used as the drying agent for organic solutions. Evaporations were done on rotary evaporators at room temperature under 5–10-mm pressure. Infrared, 100-MHz nmr, and high resolution mass spectra were obtained with Perkin-Elmer Model 21, Varian Mode. HA-100, and AEI MS-9 spectrometers, respectively. The nmr measurements were made at ambient temperature on dilute solutions containing TMS for internal standardization. Abbreviations used for nmr peak multiplicities are s (singlet), t (triplet), q (quartet), and m (multiplet). Exact mass measurements are referred to C = 12 amu. A major part of the instrumental analytical work was done by the Analytical Division of this laboratory.

10-Methyleneanthrone (4).—The standard method of synthesis for 4 involves the condensation of anthrone with formaldehyde.[16] Despite various attempts to improve this preparation,[17,18] it is still reported to give inconsistent results.[4b] In our hands the method of Barnett and Matthews[17] afforded a product containing anthraquinone as a major impurity (analysis by nmr and high resolution mass spectrometry). Recognition of this difficulty led to development of the following procedure, which consistently gave 4 containing no impurities detectable by nmr analysis.

A mixture of anthrone (25.00 g, 0.129 mol) and methanol (125 ml) was thoroughly degassed by bubbling with nitrogen and then heated to reflux, with stirring. After addition of piperidine (0.75 ml), a 37% solution of formaldehyde (35 ml, 0.47 mol) was introduced during 5 min while refluxing and nitrogen bubbling were continued. The well-stirred mixture was refluxed under nitrogen for an additional 10 min, cooled to room temperature, and allowed to stand under nitrogen until precipitation appeared complete. The crude solid was then recovered by filtration and washed several times with cold (−56°) methanol; in typical runs this solid weighed 12–15 g. Recrystallization from cyclohexane, with filtering of the hot solution to remove a small amount of an insoluble impurity, gave 8.3–10.5 g (31–39%) of pure 4 as pale golden platelets: mp 147–148° (lit.[16] mp 148°); nmr ($CDCl_3$) δ 6.22 (s, 2, $=CH_2$) and 7.3–8.4 ppm (m, 8, aromatic H).

Reaction of 4 with Triethyl Phosphite.—Triethyl phosphite (1.61 g, 9.69 mmol) was added to a slurry of finely powdered 4 (2.00 g, 9.70 mmol) in methylene chloride (2.0 ml), and the stirred mixture was gradually heated to 95° during 10 min. After an additional hour of heating (95 ± 1°) and stirring, the hot mixture was filtered. The filtrate solidified on cooling and yielded 0.30 g (14%) of 1,2-dihydro-7-ethoxy-3H-benz[*de*]anthracene-3-spiro-10′-anthrone (7a), mp 231.5–234°, upon recrystallization from aqueous ethanol. A further recrystallization (methanol–benzene) gave bright yellow microcrystals, mp 235–236°, which were shown to be identical with an authentic sample of 7a (*vide infra*) by nmr and ir spectral comparisons and a mixture melting point determination.

Reaction of 4 with Ethyl Iodide and Sodium Methoxide in Methanol.—This experiment was performed under nitrogen, using a procedure very similar to that described by Al-Khafaji.[2a] Sodium methoxide (1.60 g, 29.6 mmol) was added with stirring to a gently refluxing solution of 4 (2.00 g, 9.70 mmol) in methanol (100 ml). Ethyl iodide (30 ml, 58.5 g, 0.375 mol) was then introduced dropwise into the dark red-brown mixture during 20 min while stirring and refluxing were continued. After an additional 35 min of refluxing and stirring, the mixture (now a pale yellow solution) was concentrated at the boiling point until precipitation occurred, cooled to room temperature, and filtered. The recovered solid was washed with several small portions of cold methanol; it then weighed 1.08 g (51%) and melted at 235–238°. Two recrystallizations of the product from methanol–benzene gave pure 7a as bright yellow microcrystals: mp 236–237.5° (lit.[2a] mp 237–238°); ir (CS_2) 1668 cm^{-1} (anthrone C=O), no OH; nmr (CCl_4) δ 7.8–8.5 (m, 5; 6-, 8-, 11-, 1′-, and 8′-H), 6.6–7.5 (m, 10; 4-, 5-, 9-, 10-, 2′-, 3′-, 4′-, 5′-, 6′-, and 7′-H), 4.28 (q, 2, J = 7 Hz, OCH_2), 3.31 (poorly resolved t, 2, J = 6 Hz, CH_2Ar), 2.22 (poorly resolved t, 2, J = 6 Hz, CH_2CH_2Ar), and 1.66 ppm (t, 3, J = 7 Hz, CH_3); mass spectrum (70 eV) *m/e* 440 (too weak for accurate high resolution mass measurement, presumably $C_{32}H_{24}O_2$), 438.1600 (medium; calcd for $C_{32}H_{22}O_2$, 438.1620), and 410.1309 (strong; calcd for $C_{30}H_{18}O_2$, 410.1307).

Anal. Calcd for $C_{32}H_{24}O_2$: C, 87.24; H, 5.49. Found: C, 87.51; H, 5.60.

In a parallel experiment, a solution of 4 (1.00 g) in pure methanol (50 ml) was refluxed with stirring under nitrogen for 1.0 hr and then allowed to stand at room temperature under nitrogen overnight. The precipitated solid (0.70 g) and the methanol-soluble material (0.30 g) were recovered and examined separately by nmr. Both fractions were found to be essentially pure 4, and their spectra showed no aliphatic peaks assignable to dimeric structures.

Reaction of 10-Methylanthrone (11) with Triethyl Phosphite.—A stirred solution of 10-methylanthrone[19] (0.50 g, 2.4 mmol) and triethyl phosphite (0.41 g, 2.5 mmol) in methylene chloride (0.50 ml) was slowly heated to 95° during 8 min, kept at 95 ± 1° for 1.0 hr, cooled to room temperature, and then evaporated under vacuum. The semisolid residue (0.70 g) was not subjected to purification. However, the absence of 9-ethoxy-10-methylanthracene (12) and other 10-methylanthracene derivatives was conclusively shown by nmr analysis (C_6D_6) of the total product mixture, using a pure sample of 12 (*vide infra*) for comparison.

9-Ethoxy-10-methylanthracene (12).—This preparation was carried out under nitrogen. A 10-ml portion of a solution of potassium hydroxide (5.6 g, 0.10 mol) in absolute ethanol (100 ml) was added to 2.00 g (9.60 mmol) of 11 dissolved in absolute ethanol (20 ml), and the resulting dark red-brown solution was heated to 50°, with stirring. Diethyl sulfate (2 ml) was then added, and stirring was continued at 50° until the color of the mixture changed to pale yellow (5–10 min required). Increments of potassium hydroxide solution and diethyl sulfate were added alternately at 50° in a similar manner until all of the base and 20 ml (23 g, 0.15 mol) of the sulfate had been introduced. The last portion of base caused very little color change, an observation indicating that essentially all of 11 had reacted. After cooling to room temperature, the mixture was filtered, and the recovered solid (largely inorganic) was washed several times with fresh portions of absolute ethanol. The filtrate and washings were combined, concentrated by boiling, and diluted with water until the boiling solution exhibited a slight turbidity. Cooling yielded a precipitate, which was recovered in the usual way. This material weighed 1.80 g (79%), melted at 88.5–91.5°, and was shown to be essentially pure 12 by nmr analysis. Recrystallization of the product from aqueous methanol, followed by two recrystallizations from methanol alone, gave pale golden flakes of analytically pure material: mp 94–94.5°; ir (CS_2) no OH or C=O; nmr (CCl_4) δ 8.03–8.36 (m, 4; 1-, 4-, 5-, and 8-H), 7.24–7.49 (m, 4; 2-, 3-, 6-, and 7-H), 4.17 (q, 2, J = 7 Hz, CH_2), 2.96 (s, 3, CH_3Ar), and 1.59 ppm (t, 3, J = 7 Hz, CH_3CH_2); mass spectrum (64 eV) *m/e* 236.1202 (medium; calcd for $C_{17}H_{16}O$, 236.1201), 234.1024 (medium; calcd for $C_{17}H_{14}O$, 234.1045), and 206.0741 (strong; calcd for $C_{15}H_{10}O$, 206.0732).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.78; H, 6.81.

Reaction of Phenol with Triethyl Phosphite.—Triethyl phosphite (0.80 g, 4.8 mmol) was added to a solution of phenol (0.45 g, 4.8 mmol) in methylene chloride (1.0 ml). The well-stirred mixture was slowly warmed to 95° during 4 min and then kept at 95 ± 1° for 1.0 hr. Examination of the total product by nmr (C_6D_6) showed that a reaction (transesterification?) had occurred to some extent. However, no trace of phenetole could be detected. The absence of phenetole was confirmed by rerunning the spectrum after adding an authentic sample of the pure ether.

Oxidation of 9-Methoxy-10-methylanthracene (13) with Cupric Chloride.—A solution of the anthracene[19,20] (2.22 g, 10.0 mmol) in dry benzene (40 ml) was stirred and heated under reflux with anhydrous cupric chloride (2.69 g, 20.0 mmol) for 14.4 hr. At the end of this time HCl evolution was negligible. The hot mixture was filtered, and the recovered solid was washed several times with fresh portions of solvent. Evaporation *in vacuo* of the combined filtrate and washings left a gummy residue whose mass spectrum (70 eV) showed no peak at *m/e* 428 (parent ion for 14) and displayed only a weak peak at *m/e* 412 (a likely fragment from 14).[21] However, the spectrum did exhibit peaks assignable to 1,2-dihydro-7-methoxy-3H-benz[*de*]anthracene-3-spiro-10′-anthrone (7b, *vide infra*) at *m/e* 426.1607 (weak; calcd for $C_{31}H_{22}O_2$, 426.1620) and 410.1303 (strong; calcd for $C_{30}H_{18}O_2$, 410.1307). An nmr spectral comparison *vs.* authentic 7b (*vide infra*) indicated that this substance was one of the residue's major constituents (yield estimated from spectrum, 60–70%). Crystallization of the residue from methanol–benzene gave a reddish gum containing considerable 7b (analysis by nmr) and a second crop (0.50 g) consisting of 7b in essentially pure form (analysis by nmr and ir), mp 209–214°. Three recrystallizations of the second crop from methanol–benzene afforded a very pure sample of a low-melting form of 7b as flat orange needles, mp 221–222°. The ir and nmr spectra of this material were identical in every respect with the spectra of a higher melting form of the compound (mp 237–239°; *vide infra*).

A similar oxidation of 13 was carried out in refluxing carbon tetrachloride (reaction time, 23 hr). Product isolation was not

(16) K. H. Meyer, *Ann.*, **420**, 134 (1920).
(17) E. de B. Barnett and M. A. Matthews, *Ber.*, **59**, 767 (1926).
(18) E. Clar, *ibid.*, **69**, 1686 (1936).
(19) H. Heymann and L. Trowbridge, *J. Amer. Chem. Soc.*, **72**, 84 (1950).
(20) K. H. Meyer and H. Schlösser, *Ann.*, **420**, 126 (1920).
(21) The *m/e* 412 peak cannot be taken as evidence for the presence of a small amount of 14, since the spectrum of authentic 7b also exhibits a weak peak at *m/e* 412.

attempted; however, analysis of the crude mixture by nmr and mass spectrometry suggested that **14** was absent and that **7b** had again been formed in *ca.* 60–70% yield.

Reaction of 4 with Methyl Iodide and Sodium Methoxide in Methanol.—The procedure employed was similar to that of Al-Khafaji[2a] and essentially equivalent to that used for the analogous reaction with ethyl iodide (*vide supra*). Addition of methyl iodide (40 ml, 91 g, 0.64 mol) to a boiling solution of **4** (1.71 g, 8.29 mmol) and sodium methoxide (2.00 g, 37.0 mmol) in methanol (100 ml) required 50 min; stirring and refluxing were continued for 40 min after the addition was complete. Concentration of the pale yellow solution afforded 0.83 g (47%) of spiroanthrone **7b**, mp 229.5–232.5°. Two recrystallizations of the product from methanol–benzene gave pure **7b** as slender, bright yellow needles: mp 237–239° (lit.[2a] mp 227–228°); ir (CS_2) 1667 cm^{-1} (anthrone C=O), no OH; nmr (CCl_4) δ 7.9–8.5 (m, 5; 6-, 8-, 11-, 1′-, and 8′-H), 6.7–7.6 (m, 10; 4-, 5-, 9-, 10-, 2′-, 3′-, 4′-, 5′-, 6′-, and 7′-H), 4.14 (s, 3, CH_3), 3.33 (poorly resolved t, 2, J = 6 Hz, CH_2Ar), and 2.24 ppm (poorly resolved t, 2, J = 6 Hz, CH_2CH_2Ar); mass spectrum (70 eV) *m/e* 426.1607 (weak; calcd for $C_{31}H_{22}O_2$, 426.1620) and 410.1300 (strong; calcd for $C_{30}H_{18}O_2$, 410.1307).

Anal. Calcd for $C_{31}H_{22}O_2$: C, 87.30; H, 5.20. Found: C, 87.44; H, 5.26.

Recrystallization of 0.10 g of pure **7b** (mp 237–239°) from methanol–benzene, using the low-melting form of **7b** (*vide supra*) for seeding, gave 0.08 g of flat orange needles that melted sharply at the lower temperature.

Oxidation of 4 with Molecular Oxygen.—A suspension of **4** (0.50 g, 2.4 mmol) in dry benzene (3.0 ml) was degassed by the freeze–thaw method and then stirred rapidly (magnetic bar) in the dark at 24–25° under an atmosphere of pure oxygen. After 122.4 hr the total absorbed oxygen amounted to 24.7 ml (volume corrected to 0° and 760 mm, 1.10 mmol), and at this point the rate of oxygen uptake had decreased to a negligibly small value. The final reaction mixture had a strong formaldehyde odor and contained a white solid, which was recovered by filtration and washed several times with fresh benzene. This solid (fraction A) weighed 0.07 g and gave a doubtful positive test for peroxide(s) with potassium iodide in acetic acid. Evaporation of the combined filtrate and washings yielded 0.50 g of pale yellow powder (fraction B), whose peroxide test was definitely positive. Analysis by nmr showed that fractions A and B contained anthraquinone (**17**), spiro[anthracene-9(10H),2′-oxiran]-10-one (**18**), and **4**; these identifications were confirmed by nmr peak enhancements resulting from addition of the pure substances. Fraction B also contained a material that exhibited a sharp singlet at δ 2.14 ppm ($CDCl_3$). Double verification was obtained for the presence of **18** by adding the authentic epoxide[22] to solutions of B in two different solvents ($CDCl_3$, C_6D_6). Enhancement of a singlet assigned to the methylene protons of **18** (δ 3.38 ppm in $CDCl_3$, 2.67 ppm in C_6D_6) occurred in both cases, and enhancement of several aromatic peaks was also observed. The mass spectrum (70 eV) of fraction A showed strong parent peaks for **17** and **4** at *m/e* 208.0534 (calcd for $C_{14}H_8O_2$, 208.0524) and 206.0734 (calcd for $C_{15}H_{10}O$, 206.0732), respectively. The mass spectrum (70 eV) of fraction B also contained intense parent peaks for **17** (*m/e* 208.0534) and **4** (*m/e* 206.0748), as well as a weak parent peak for **18** (*m/e* 222.0665; calcd for $C_{15}H_{10}O_2$, 222.0681. The parent peak of pure **18** was shown to be weak at 70 eV). Quantitative calculations based on the nmr spectrum showed that the composition of fraction A was **17**, 77%; **18**, 4%; **4**, 19%. On the assumption that the material resonating at 2.14 ppm was peroxide **16**, the composition of fraction B was estimated by nmr as **16**, 19%; **17**, 23%; **18**, 37%; **4**, 21%. Thus the total yields of **16**, **17**, **18**, and recovered **4** were estimated to be 17, 34, 35, and 23%, respectively.

An attempt to reproduce the published preparation[11] of **16** gave none of the desired product.

Registry No.—**4**, 4159-04-0; **7a**, 24165-82-0; **7b**, 24215-76-7; **12**, 24165-83-1.

Acknowledgment.—The author is indebted to Mr. H. J. Tarski for excellent technical assistance, and to Dr. H. G. Schutze for strong administrative support.

(22) G. L. Buchanan and D. B. Jhaveri, *J. Org. Chem.*, **26**, 4295 (1961); J. Rigaudy and L. Nédélec, *Bull. Soc. Chim. Fr.*, 400 (1960).

Reaction of a Quinone Methide with Tri-*n*-butylphosphine[1]

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Quinone methide **2** reacts with tri-*n*-butylphosphine in benzene or *n*-heptane solution to form an isolable inner salt, (3,5-di-*t*-butyl-4-oxybenzyl)tri-*n*-butylphosphonium betaine (**4**). Betaine **4** can also be prepared by dehydrochlorination of phosphonium chloride (**3**) with methanolic sodium methoxide. The betaine retains its structure in polar solvents (methanol, ethanol, dimethyl sulfoxide, or acetone), but, when warmed with relatively nonpolar solvents (benzene, toluene, *p*-dioxane, or cyclohexene), it decomposes to form bisphenol **9** and tri-*n*-butylphosphine as major products. Decomposition of **4** in the presence of benzaldehyde gives considerable amounts of stilbenol **8** and tri-*n*-butylphosphine oxide; decomposition in the presence of chloroprene gives, *inter alia*, spirotrienone **13**. These observations and the results of experiments with model compounds suggest that the decomposition of **4** probably produces ylide **5** and quinone methide **2**, *in situ*, and that bisphenol **9** then results from a sequence involving addition of **5** to **2**, followed by prototropic shifts and loss of tri-*n*-butylphosphine. The reactions of quinone methide **2** with triethyl phosphite and tri-*n*-butylphosphine are briefly compared.

Observations made during the course of previous work[3] suggested that quinone methides were involved as reactive intermediates during the inhibition of autoxidation by certain synergistic antioxidant systems containing hindered phenols and compounds of trivalent phosphorus. It appeared that separate investigations of quinone methide–phosphorus(III) nucleophile reactions might provide insight into the overall inhibition process, and this supposition prompted an examination of the reaction of triethyl phosphite with quinone methide **2**.[4] Since the results of that study were both interesting and unexpected,[4] we felt that information about the behavior of **2** toward other trivalent phosphorus nucleophiles would be desirable for purposes of comparison. The reaction of **2** with tri-*n*-butylphosphine was therefore investigated, and the present paper describes the results obtained. To our knowledge, no other reactions of quinone methides with phosphines have previously been described in the literature.

(1) (a) Paper VII of a series on oxidation inhibitors. (b) Paper VI: W. H. Starnes, Jr., *J. Org. Chem.*, **35**, 1974 (1970). (c) Presented at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 25, 1970.

(2) Summer employee, 1968.

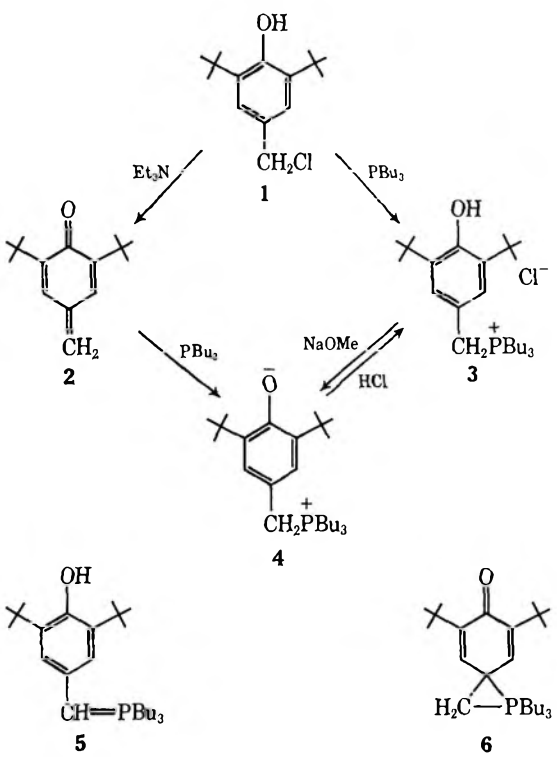
(3) W. H. Starnes, Jr., and N. P. Neureiter, *ibid.*, **32**, 333 (1967).

(4) W. H. Starnes, Jr., J. A. Myers, and J. J. Lauff, *ibid.*, **34**, 3404 (1969).

Results and Discussion

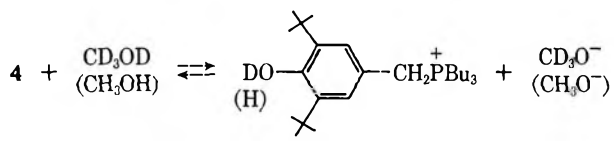
Quinone methide **2**, an unisolable species,[5] was generated *in situ* by allowing chloromethylphenol **1** to react with triethylamine in hydrocarbon solvents[5c,6] (Scheme I). Dropwise addition of tri-*n*-butylphosphine (1 mol equiv) to a dilute solution of **2** (0.027 *M*) in *n*-heptane caused a vigorous reaction leading to immediate precipitation of a solid product. The solid was shown by various analyses to be a 1:1 adduct (yield, 87%) of the phosphine and the quinone methide; it was also formed in benzene under similar conditions.

SCHEME I



Mechanistic preconceptions suggested that the adduct could be prepared independently *via* the alternative route shown in Scheme I. This expectation was readily confirmed. Alkylation of tri-*n*-butylphosphine with chloromethylphenol **1** gave phosphonium chloride **3** in 97% yield. Addition of excess sodium methoxide to a methanol solution of **3**, followed by addition of water, afforded a white precipitate (yield, 84%) that was identical with the adduct obtained directly from **2**. The adduct was converted to its alternative precursor, **3** (yield, 90%) by treatment with dry HCl in methanol. These observations were considered to provide definitive evidence for attack by tri-*n*-butylphosphine on the methylene group of **2**.

At this point three possible structures for the adduct (**4**, **5**, and **6**) seemed worthy of consideration. Though fairly stable *in vacuo*, the substance underwent slow oxidative decomposition on exposure to air, an observation tending to exclude structure **6**. The material's lack of color argued against the ylide formulation[7] **5**, and its solubility properties (soluble in polar organic solvents, slightly soluble in water, insoluble in solvents of low polarity) were clearly more compatible with the betaine structure (**4**) than with either of the alternatives.[7] The high-resolution mass spectrum of the compound showed strong peaks corresponding to the parent *m/e* values for **2** and tri-*n*-butylphosphine, a result verifying neither structure but perhaps comprising a modicum of evidence against **5**. Stronger evidence in favor of **4** was forthcoming from the ir spectrum (Nujol) which showed no bands attributable to OH or C=O absorption. Furthermore, nmr measurements provided excellent evidence for equilibration of **4** with its conjugate acid (**7**) in methanol-d_4, and the existence of this equilibrium was strongly supported by uv studies on solutions of the adduct in methanol and methanolic sodium methoxide. The nmr results also showed that, in methanol-d_4, the benzyl protons of **4** were quickly replaced by deuterium. This observation suggested the possible presence of low equilibrium concentrations of ylide **5** and/or its conjugate anion; however, no independent evidence was obtained for the formation of these species in methanol solution. Low-temperature ir measurements showed that the adduct did not cyclize to the spirodienone structure **6** in ethanol at −93°,[8] and further studies by nmr showed that the betaine structure was also retained in methanol-d_4 at −90° and in dimethyl sulfoxide-d_6 or acetone-d_6 at room temperature. All available information thus indicates that the adduct has the betaine structure, **4**, in the solid state and in solvents of relatively high polarity.



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Inner salt tautomers of phosphonium ylides have frequently been postulated as reactive intermediates, but only a few substances of this type have actually been isolated heretofore. Of particular interest in this regard are the 1:1 adducts formed from 3-benzylidene-2,4-pentanedione and trialkyl- or dialkylphenylphosphines.[9] The enhanced stability of these isolable betaines relative to that of other possible isomers (ylides or cyclized structures containing pentavalent phosphorus) evidently results from the cooperative interaction of several favorable factors; *viz.*, relatively low anion basicity due to resonance stabilization, relatively low acidity of benzyl hydrogen caused by the presence of electron-donating substituents on phosphorus, steric hindrance to bimolecular prototropy, and the necessity of placing a relatively electropositive carbon substituent in an apical position of phosphorus(V) (an energetically

(5) (a) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, No. 25, 9 (1960); (b) R. H. Bauer and G. M. Coppinger, *Tetrahedron*, **19**, 1201 (1963); (c) N. P. Neureiter, *J. Org. Chem.*, **28**, 3486 (1963); (d) B. R. Loy, *ibid.*, **31**, 2386 (1966).

(6) W. H. Starnes, Jr., *ibid.*, **31**, 3164 (1966).

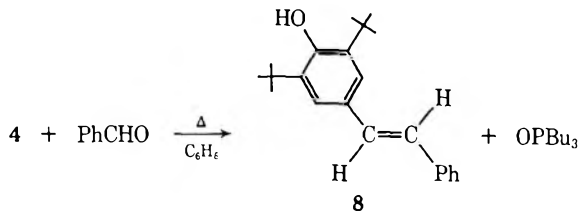
(7) *Cf.* A. W. Johnson, "Ylid Chemistry," Academic Press Inc., New York, N. Y., 1966, p 63.

(8) No carbonyl absorption could be detected under these conditions. Carbonyl absorption is observed in the 1610–1655-cm^{-1} region for analogous spirodienones containing carbon in place of phosphorus: G. A. Nikiforov, B. D. Sviridov, and V. V. Ershov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 542 (1968).

(9) F. Ramirez, J. F. Pilot, and C. P. Smith, *Tetrahedron*, **24**, 3735 (1968).

unfavorable arrangement[9,10]) in order for cyclization to occur. The stability of **4** relative to that of **5** and **6** can be rationalized on similar grounds; moreover, one notes that in this case the cyclized structure **6** should also be disfavored by the absence of aromatic resonance and by the presence of steric strain associated with the three-membered ring.

Since betaine **4** was obviously more polar than either of its possible isomers, it appeared that isomerization of the betaine might occur if the substance could be brought into solution in solvents of low polarity. In order to investigate this possibility, betaine **4** was heated under reflux with a solution of benzaldehyde (1.0 mol equiv) in benzene. The betaine quickly dissolved, and after 1.5 hr of heating the mixture afforded *trans*-3,5-di-*t*-butyl-4-stilbenol (**8**, 55%) and tri-*n*-



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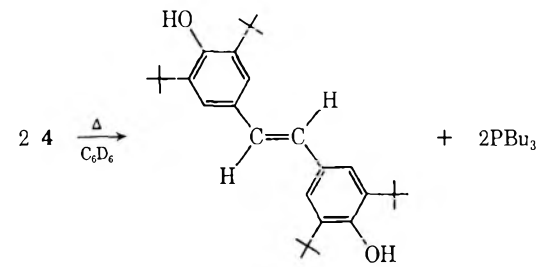
butylphosphine oxide (crude yield, 83%) on work-up. These are the products to be expected from a typical Wittig reaction; thus their presence can be taken as evidence for rearrangement of **4** to ylide **5** under the reaction conditions. In a related experiment, a benzene solution of quinone methide **2** (1.0 mol equiv) was slowly added to a stirred solution of tri-*n*-butylphosphine (1.0 mol equiv) and benzaldehyde (1.1 mol equiv) in benzene at 50°. Under these conditions formation of **4**, isomerization of **4** to **5**, and entrapment of **5** with benzaldehyde were all evidently accomplished concurrently, since stilbenol **8** and tri-*n*-butylphosphine oxide were again found to be major reaction products (isolated yields were 58 and 73%, respectively).

Betaine **4** was allowed to react with *n*-heptaldehyde in benzene under a variety of conditions. Tri-*n*-butylphosphine oxide was formed in every case, and the presence of the other Wittig product, 2,6-di-*t*-butyl-4-(1-octen-1-yl)phenol, was strongly suggested by mass spectrometric analysis. However, the pure alkenyl phenol (a mixture of *cis* and *trans* isomers?) could not be isolated. Attempts were also made to carry out Wittig reactions with betaine **4** and a variety of ketones (diethyl ketone, acetophenone, benzophenone), but these experiments gave little (if any) of the desired olefinic products. The transient intermediate responsible for olefin formation was thus shown to be a highly selective species whose reactivity toward carbonyl compounds resembled the reactivity previously reported for phosphonium ylides containing resonance-stabilized carbanion moieties.[11] This observation was consistent with our formulation of the intermediate as **5**, although the intermediate's total inertness toward ketones was still somewhat surprising. Realizing that a rapid side reaction could be partly responsible for this apparent lack of affinity, we next attempted to identify the other products formed from **4** under conditions conducive to its isomerization.

(10) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968), and references cited therein.

(11) For references to related cases and a comprehensive mechanistic rationale, see ref 7, pp 152–171.

Mass spectrometric analysis of crude product mixtures obtained from "Wittig reactions" of **4** showed that a by-product with molecular formula $C_{30}H_{44}O_2$ had been formed in every case. Since a by-product having this composition could only result from a bimolecular process involving two molecules of **4**, separate studies of the decomposition of **4** were clearly in order. Samples of the betaine were therefore warmed in benzene-d_6 until complete dissolution occurred, and the solutions were then analyzed immediately by nmr and vpc. The analyses showed that bisphenol **9** ($C_{30}H_{44}O_2$) and tri-*n*-butylphosphine had been formed in yields amounting to *ca.* 80% and 95–100%, respectively. Minor by-products were also detected (but



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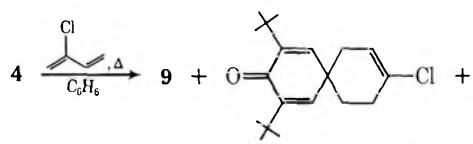
not identified), and analogous decompositions of the betaine in *p*-dioxane, toluene-d_8, or cyclohexene were found to give similar results. The reaction in cyclohexene gave no detectable by-products derived from the solvent, an observation militating against an already unlikely route to **9** involving dimerization of a carbene. Decompositions of betaine samples containing two benzyl deuteriums (*vide supra*) gave bisphenol-**9**-d_4 labeled at the hydroxyls and the vinyl positions.

A plausible mechanism for the decomposition of **4** is shown in Scheme II. This mechanism is consistent with several items of information. In an attempt to secure direct evidence for reversion of **4** to its precursors (eq 1, Scheme II), the betaine was decomposed in benzene containing a large excess of chloroprene. This reaction gave spirotrienone **13** and bisphenol **14**, to-



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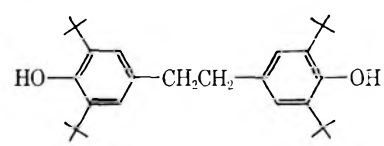


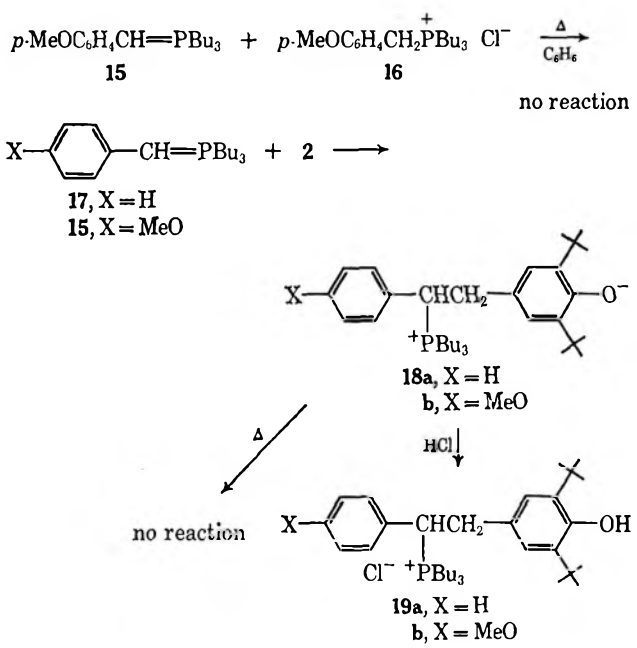
14

gether with bisphenol **9** and unidentified products. The formation of **13** constitutes good evidence for the intermediacy of quinone methide **2**, since the Diels–Alder reaction of chloroprene and **2** is known to be facile,[12] and no other reasonable routes to **13** are apparent. Quinone methide **2** could also have been the precursor of bisphenol **14**,[13] *via* a process involving the corresponding bisphenoxy radical.[5b–d]

(12) J. D. McClure, *J. Org. Chem.*, **27**, 2365 (1962).

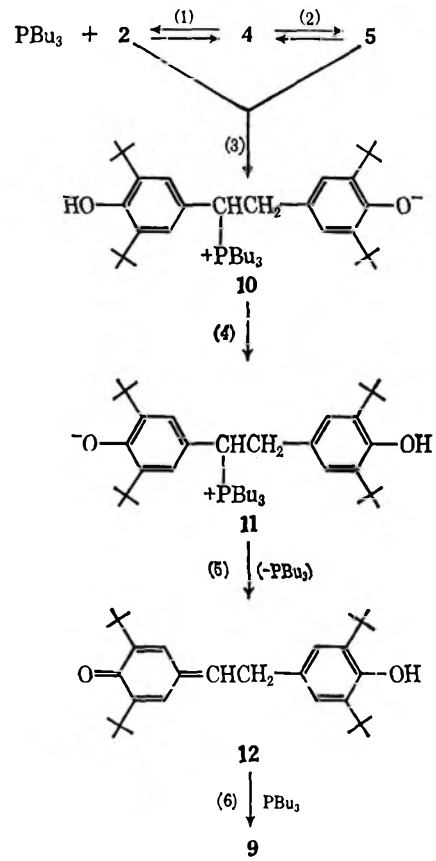
(13) Vpc analyses suggested that small amounts of **14** were also produced in betaine decompositions performed without chloroprene. However, in these experiments **14** was neither isolated nor characterized.

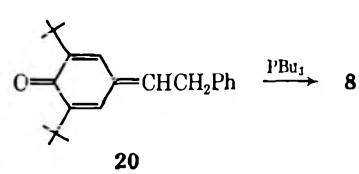
Since the spontaneous free-radical dimerization of **2** does *not* give bisphenol **9**,[5b,c] the coupling process leading to **9** is clearly best considered to involve nucleophilic displacement or addition. Ylide **5**, a highly nucleophilic species, is probably formed from **4** (eq 2) under the reaction conditions (*vide supra*). Betaine **10** could be formed by reaction of **5** with **2** (eq 3, Scheme II), or by reaction of **5** with **4** in a process involving SN2 displacement of tri-*n*-butylphosphine. However, an equimolar mixture of ylide **15** and phosphonium chloride **16** failed to react after 16.4 hr in benzene at 50°—a result that made the SN2 route to **10** seem highly unlikely. In contrast, eq 3 of Scheme II was expected to occur with ease,[14] and this supposition was supported by the behavior of quinone methide **2** toward ylide **17**, an analog of ylide **5**. In benzene at room temperature the reaction with **17** was rapid and essentially quantitative; it afforded an adduct that was isolated as the hydrochloride (**19a**) after treatment with HCl. A reaction of **2** with ylide **15** gave a similar result; however, in this case the product hydrohalide (**19b**) was not purified.



Although direct conversion of **10** to **9** seemed possible *a priori*, experiments with betaines **18a** and **18b** showed that this type of β elimination was not a favored process. Benzene solutions of **18a** and **18b** still afforded practically quantitative yields of the corresponding hydrochlorides (**19a** and **19b**) even after extended periods of refluxing (up to 92.5 hr), and an identical result was obtained in a similar experiment where equimolar amounts of **18a** and **19a** were employed.[15] Since the preparations of **18a** and **18b** had involved dehydrohalogenation of phosphonium chlorides with *n*-butyllithium, it also seemed advisable to show that complexation with lithium chloride[16] could not have been responsible for the high stabilities of the two betaines in question. Phosphonium chloride **3** was therefore allowed to react with *n*-butyllithium (1.0 mol equiv) in benzene at room temperature, and the resulting mixture (which presumably contained **4** and lithium chloride) was heated under reflux for 1.0 hr. As expected, a considerable amount of bisphenol **9** was formed. The inherent stability of **10** thus appears to be much less than that of **18a** or **18b**, a result making an indirect conversion of **10** to **9** (Scheme II, eq 4–6) seem an attractive possibility. Loss of tri-*n*-butylphosphine from betaine **11** (eq 5, Scheme II) appears quite reasonable by analogy with eq 1 of Scheme II, and the phosphine-catalyzed isomerization of quinone methide **12** (eq 6, Scheme II) is consistent with previous observations relating to this quinone methide's base-catalyzed isomerization.[4] In an indirect test for the feasibility of eq 6 of Scheme II, quinone methide **20** was subjected to the action of tri-*n*-butylphosphine in benzene. This experiment gave the anticipated result: quantitative formation of stilbenol **8** in an extremely rapid reaction. Scheme II thus appears to conform with all relevant facts, although information about certain mechanistic details is lacking.[17]

SCHEME II





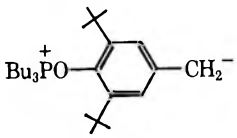
(14) *Cf.* H. J. Bestmann and H. J. Lang, *Tetrahedron Lett.*, 2101 (1969).

(15) Under the conditions of these experiments, betaines **18a** and **18b** might have been converted (at least in part) to the corresponding ylide isomers. However, this rearrangement would not invalidate the use of **18a** and **18b** as models for testing the direct conversion of **10** to **9**, since isomerization to an ylide is a potential reaction path for **10** also.

(16) *Cf.*, *inter alia*, ref 7, p 135 and 136 and literature cited therein; also R. F. Hudson, "Structure and Mechanism in Organo-phosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, p 225.

(17) For example, reversal of eq 2 of Scheme II has not been demonstrated experimentally.

We now wish to consider the possibility of an alternative mechanism for decomposition of **4** involving betaine **21** as the nucleophilic intermediate. Betaine **21** could result from addition of tri-*n*-butylphosphine



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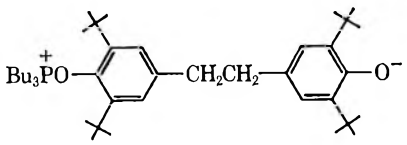

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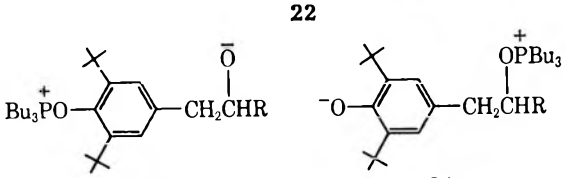
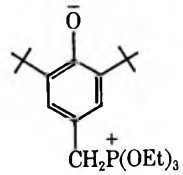


23 **24**

to **2** in a reaction competitive with the reverse process of eq 1 of Scheme II. Addition of **21** to a second molecule of **2** would give a dimeric betaine (**22**) which might decompose to quinone methide **12** and tri-*n*-butylphosphine. Phosphine-catalyzed isomerization of **12** to **9** would then complete the reaction sequence. A mechanism involving betaine **21** can also account for the formation of Wittig products from aldehydes and **4**. Reaction of **21** with an aldehyde would give betaine **23**, a species which might rearrange into betaine **24**. Tri-*n*-butylphosphine oxide and an alkenylphenol could then result from fragmentation of **24**, *via* a process formally depicted as an internal β elimination.

Although schemes involving **21** have not been excluded experimentally, these mechanisms seem improbable for a number of reasons. To the extent that reaction rates are influenced by the resonance stabilizations of products, formation of stilbenols by fragmentation of betaines **18a** and **18b** appears much more likely than formation of quinone methide **12** by fragmentation of betaine **22**. Betaines **18a** and **18b** were actually found to be quite *stable* toward fragmentation; thus on this basis the possibility that **22** would give **12** appears remote indeed. Furthermore, the nucleophilic intermediate's high selectivity toward carbonyl compounds appears more compatible with structure **5** than with structure **21**, since **21** should be a very reactive species having low discriminative ability. Finally, we note that there is no extant evidence for addition of a trivalent phosphorus nucleophile to the carbonyl group of a *p*-quinone methide,[1b,4] the reaction of triethyl phosphite with quinone methide **2** having been conclusively shown not to involve a process of this type.[4]

The reactions of quinone methide **2** with triethyl phosphite[4] and tri-*n*-butylphosphine can now be compared in detail. At room temperature in relatively nonpolar media these reactions give entirely different types of isolable products. Nevertheless, mechanistic studies[4] have shown that the initial intermediate in the phosphite reaction is betaine **25**, a species analogous to **4**. Since triethyl phosphite is a relatively weak nucleophile (weaker than the phosphine),[18] formation of **25** is relatively slow.[4,19] On the other hand, rearrangement of **25** into the corresponding ylide should be



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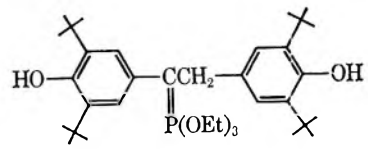

26

relatively fast (faster than the rearrangement of **4** to **5**), owing to the presence of three relatively electronegative groups on phosphorus.[20] Thus, as a consequence of these kinetic features, betaine **25** is destined to remain a reactive intermediate,[4] while betaine **4** is an isolable species. However, at slightly elevated temperatures, betaine **4** gives bisphenol **9** *via* a mechanism (Scheme II) which is probably closely analogous to the mechanism of formation of **9** from **2** in the reaction with triethyl phosphite.[4] The phosphite reaction also affords significant amounts of a trimer of **2**, *via* a mechanism involving ylide **26** as a key intermediate,[4] whereas little (if any) trimer is formed in the decomposition of betaine **4**. These divergent results suggest that betaines **10** and **11** are converted into their ylide isomer (the analog of **26**) at relatively slow rates, a circumstance which could be occasioned by the presence of electron-donating alkyl groups on phosphorus.[20] Finally, we note that relatively high concentrations of quinone methide **12** could be reached in the reaction of **2** with triethyl phosphite[4] but not in the analogous reaction (decomposition of **4**) involving tri-*n*-butylphosphine. This dissimilarity probably reflects differences in the rate of conversion of **12** to **9** and may thus be related to the different basicities (or nucleophilicities toward hydrogen) of the trivalent phosphorus reagents.[21]

Summarizing the foregoing remarks, we conclude that the overall reactions of quinone methide **2** with triethyl phosphite and tri-*n*-butylphosphine are probably quite similar mechanistically, and that the observed differences between these reactions with regard to product type are rationalizable in terms of differences in the rates of corresponding mechanistic steps. The rate differences appear to be consistent with the relative nucleophilicities and basicities of the phosphite and the phosphine, and with the expected effects of substituent electronegativity on rates of ylide formation.

(18) (a) This order of reactivity has been established for displacements on saturated carbon, and it is commonly assumed to hold for other types of reactions involving nucleophilic attack by trivalent phosphorus reagents. (b) See A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., Amsterdam, 1967, pp 15–17, 37, and 38, and references cited therein. (c) Tri-*n*-butylphosphine is said to be more reactive than trimethyl phosphite toward an olefinic carbon atom of *trans*-dibenzoylethylene: F. Ramirez, O. P. Madan, and C. P. Smith, *Tetrahedron*, **22**, 567 (1966).

(19) Consideration should also be given to the possibility that **4** and **25** are formed reversibly. If this is indeed the case, the equilibrium constant for formation of **25** should be much less than that for formation of **4**, owing to the different nucleophilicities of the trivalent phosphorus reagents.

(20) For a brief discussion of the effects of phosphorus substituents on ease of ylide formation, see ref 7, p 13.

(21) Toward protons, tri-*n*-butylphosphine is reported to be a stronger base than triethyl phosphite: C. A. Streuli, quoted by L. S. Meriwether and M. L. Fiene, *J. Amer. Chem. Soc.*, **81**, 4200 (1959). A rough estimate of the basicity of tri-*n*-butyl phosphite provides further support for the conclusion that trialkyl phosphites are weaker bases than trialkylphosphines (ref 18b, p 15).

Experimental Section[22]

Materials.—Tri-*n*-butylphosphine contained no impurities detectable by vpc or nmr analysis and was used as received; we are indebted to Carlisle Chemical Works, Inc., for a generous gift of this material. Benzene (B & A ACS reagent grade), *n*-heptane (reagent grade, Humble Oil and Refining Co.), and *p*-dioxane (Matheson Coleman and Bell Spectroquality grade) were dried over sodium ribbon and stored under nitrogen. Cyclohexene (Phillips "Pure" grade) was percolated over alumina just prior to use. Benzaldehyde, *n*-heptaldehyde, and chloroprene were redistilled under nitrogen and used immediately after purification. *n*-Butyllithium was obtained from Foote Mineral Co. as a solution in hexane and was used as received. Gaseous HCl was dried by passage through H_2SO_4. All other chemicals used were highly purified articles of commerce. Purities were verified by spectral measurements, vpc analyses, and the determination of appropriate physical constants.

Instrumental Analysis.—Ultraviolet, 100-MHz nmr, and high resolution mass spectra were recorded with Cary Model 14, Varian Model HA-100, and AEI MS-9 spectrometers, respectively. The nmr measurements were made at ambient temperature (except where noted otherwise) on dilute solutions containing TMS as the internal standard. Nmr peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), dt (doublet of triplets), m (multiplet). Exact mass measurements are referred to C = 12 amu. Conventional ir spectra were obtained with a Perkin-Elmer instrument, Model 21; low-temperature ir measurements were made with a Beckman IR-12 spectrometer equipped with a VLT-2 variable low temperature unit. Programmed temperature vpc analyses were done with an F & M instrument (Model 500) equipped with a 6 ft × 0.25 in. (o.d.) stainless steel column containing SE-30 (5%) on 40–60 mesh Chromosorb W, acid washed, DMCS treated. The carrier gas was helium; column temperature was increased from 100 to 350° at the rate of 8°/min. Vpc peak areas were measured with a planimeter.

(3,5-Di-*t*-butyl-4-oxybenzyl)tri-*n*-butylphosphonium Betaine (4) from 4-Methylene-2,6-di-*t*-butyl-2,5-cyclohexadien-1-one (2) and Tri-*n*-butylphosphine.—A solution of quinone methide **2** (2.0 mmol) in *n*-heptane (75 ml) was prepared by dehydrochlorination of chloromethylphenol **1** (0.51 g, 2.0 mmol) with triethylamine (0.21 g, 2.1 mmol) according to a previously described procedure.[6] The solution was degassed by stirring and bubbling with nitrogen; then 0.41 g (2.0 mmol) of tri-*n*-butylphosphine was added dropwise during 2 min while stirring and nitrogen bubbling were continued. A precipitate of **4** appeared immediately. Stirring with introduction of nitrogen was continued for 5 min more. The betaine was then recovered by suction filtration, washed thoroughly on the filter with several portions of petroleum ether (bp 30–60°) and ether, and dried overnight at room temperature under vacuum (*ca.* 5 mm). The pale lavender solid thus obtained weighed 0.73 g (87%) and melted at 92–94° (pale blue-green melt); spectral comparisons showed it to be identical with a sample of betaine **4** prepared by the alternative route described below. Reactions of quinone methide **2** with tri-*n*-butylphosphine in benzene gave similar results.

(3,5-Di-*t*-butyl-4-hydroxybenzyl)tri-*n*-butylphosphonium Chloride (3).—Tri-*n*-butylphosphine (40.60 g, 0.201 mol) was added dropwise during 0.5 hr to a stirred solution of chloromethylphenol **1** (50.96 g, 0.200 mol) in benzene (500 ml). After an additional 0.7 hr of stirring, the mixture was allowed to stand undisturbed for 5.3 hr and then filtered with suction. The recovered solid was washed twice with benzene and then twice with ether; after drying *in vacuo* at 60° it weighed 89.2 g (97%), melted at 183–184°, and contained no impurities that could be detected by nmr analysis. Recrystallization of a small sample from toluene gave **3** as tiny white flakes: mp 186–187°; ir (Nujol) 3600 cm^{-1} (weak, sharp, hindered phenol OH); nmr (CD_3OD) δ 7.11 (d, 2, J = 3 Hz, aromatic H), 3.68 (d, 2, J = 14 Hz, CH_2Ar), 1.97–2.37 (m, 6, 3 CH_2Pr), 1.26–1.72 (m with strong s at 1.45 ppm, 30, 3 $CH_2CH_2CH_3$ and 2 *t*-Bu), and 0.97 ppm (highly distorted t, 9, $J \cong 7$ Hz, 3 CH_2CH_3); for uv spectrum, see Table I.

Anal. Calcd for $C_{27}H_{50}ClOP$: C, 70.94; H, 11.03; Cl, 7.76; P, 6.78. Found: C, 70.91; H, 11.17; Cl, 7.94; P, 6.63.

Betaine 4 from Phosphonium Chloride (3).—A solution of **3** (1.15 g, 2.52 mmol) in methanol (5 ml) was degassed by stirring and bubbling with nitrogen. Sodium methoxide (0.41 g, 7.6 mmol) was then added, and after an additional 5 min of stirring and bubbling, the mixture was poured into water (50 ml), stirred until precipitation appeared to be complete (*ca.* 5 min), and filtered using suction. The solid was quickly washed in succession with water (three portions) and dry ether (four portions), then dried under vacuum (*ca.* 5 mm) to give 0.89 g (84%) of **4** as white microcrystals: mp 92–94° (pale blue-green melt; very slow rates of heating gave melting points that were lower by 3–4°); soluble in methanol, ethanol, dimethyl sulfoxide, or acetone; sparingly soluble in water; insoluble at room temperature in petroleum ether (bp 30–60°), ether, benzene, toluene, *p*-dioxane, or carbon tetrachloride; ir (Nujol) no OH or C=O; ir (EtOH) no C=O at temperatures ranging from 25 to −93°; nmr (CD_3OD) δ 6.85 (d, 2, J = 3 Hz, shifts upfield upon addition of NaOMe, aromatic H), 3.45 (d, 2, J = 13 Hz, disappears after 2–2.5 hr of standing due to D exchange with solvent, CH_2Ar), 1.87–2.26 (m, 6, 3 CH_2Pr), 1.26–1.74 (m with strong s at 1.41 ppm, 30, 3 $CH_2CH_2CH_3$ and 2 *t*-Bu), and 0.97 ppm (highly distorted t, 9, $J \cong 7$ Hz, 3 CH_2CH_3); nmr (CD_3OD, −90°) equivalent to spectrum in CD_3OD at room temperature, except for line broadening and loss of fine structure due to viscosity effects; nmr [$(CD_3)_2SO$ or $(CD_3)_2CO$] similar to spectrum in CD_3OD; mass spectrum (64 eV) *m/e* 218.1670 (strong; calcd for $C_{15}H_{22}O$, 218.1671) and 202.1837 (strong; calcd for $C_{12}H_{27}P$, 202.1850).

Anal.[23] Calcd for $C_{27}H_{49}OP$: C, 77.09; H, 11.74. Found: C, 76.87; H, 11.79.

The uv spectra of betaine **4** and two related compounds are presented in Table I. On the basis of these data and published uv data for 2,6-di-*t*-butylphenols containing *para* substituents which do not undergo strong resonance interaction with the ring,[24] the maxima at 269 and 300 mμ may be assigned to the phenolate moiety of **4**, while the maxima at 234 and 276–282 mμ can be ascribed to the cation **7** resulting from protonation of the betaine by methanol. In pure methanol the log ε values obtained for **4** are strongly dependent on betaine concentration (*cf.* the two tabulated values of log ε for the 300-mμ band), owing to concentration effects on the position of the equilibrium be-

TABLE I

ULTRAVIOLET SPECTRA[a]

	MeOH		0.5 *M* NaOMe, MeOH	
Compd	λ_{max},[b] mμ	Log ε	λ_{max},[b] mμ	Log ε
4[c]	234	3.95[d]	234[e,f]	3.62
	276	3.28[g]	269	4.13
	282[e]	3.23[g]	300[e]	3.71
	300[e]	2.31[g]	365[h]	2.54[h]
	300[e]	2.87[i]		
	365[j]	2.18[j,k]		
3	234	3.94	234[e,f]	3.69
	276	3.19	269	4.16
	282[e]	3.17	300[e]	3.73
			365[l]	1.67[l]
16	231	4.18	231	4.19
	278	3.18	278	3.18
	284	3.12	284	3.12

[a] From 220 to 500 mμ unless noted otherwise. [b] ±1 mμ, wavelength scale not calibrated. [c] Region scanned, 220–400 mμ. [d] [**4**] = 5.16 × 10^{-5} *M*. [e] Shoulder. [f] Presence uncertain; may have been an instrumental artifact. [g] [**4**] = 5.16 × 10^{-4} *M*. [h] Bisphenol **9**, 5.0 mol %. [i] [**4**] = 2.58 × 10^{-3} *M*. [j] Bisphenol **9**, 5.0 mol % (calculated from spectrum in 0.5 *M* methanolic NaOMe). [k] [**4**] = 5.16 × 10^{-3} *M*. [l] Bisphenol **9**, 0.7 mol %.

(22) Boiling points and melting points are uncorrected. The melting points were determined with a Fisher-Johns apparatus. Unless noted otherwise, elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Drierite was used as the drying agent for organic solutions. Distillations were done with a spinning-band column (24 in. × 8 mm); evaporations were carried out on rotary evaporators at room temperature under 5–10 mm of pressure. A major part of the instrumental analytical work was performed by the Analytical Division of this laboratory.

(23) Macrocombustion analysis was by Mr. E. Bowers, Humble Oil and Refining Co., Baytown, Texas.

(24) L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, **85**, 3397 (1963); C. H. Rochester, *J. Chem. Soc.*, 676 (1965).

tween **4** and **7**. Rapid equilibration would cause time averaging of the chemical shifts and thus accounts for the relatively simple nmr spectrum observed for **4** in CD_3OD. Addition of methoxide ion increases the **4**:**7** ratio, thereby enhancing the average shielding experienced by the aromatic protons and causing their resonance position to shift upfield (*vide supra*). In 0.5 *M* methanolic NaOMe different samples of **4** gave values of log ϵ (365 mμ) ranging from 2.54 to 2.86. This observation, together with the much lower value of log ϵ (365 mμ) obtained for betaine samples generated *in situ* from **3**, suggested that the 365-mμ band was produced by an impurity. Stilbenediol[25] **9** was obviously a possible contaminant, and indeed, the uv spectrum of this phenol in 0.5 *M* methanolic NaOMe was found to contain a strong band at 365 mμ. This band is evidently produced by an anionic species, since it does not appear in the spectrum of **9** in pure methanol. Its presence in the spectrum of **4** in pure methanol thus indicates proton transfer from **9** to the betaine's phenoxide moiety. A $\pi \rightarrow$ d or $\pi \rightarrow \pi^*$ transition involving the C=P chromophore[26] of ylide **5** was also considered as a possible explanation for the presence of the 365-mμ band; however, this rationale appears unacceptable in view of the absence of the band from the spectrum of phosphonium chloride **16** under basic conditions. In 0.5 *M* methanolic NaOMe the 365-mμ band of pure **9** has log ϵ 3.84, this value was used to compute the mole per cent of **9** present in samples of **3** and **4**.

In air betaine **4** slowly decomposes to an amorphous purple mass. Storage under vacuum reduces the rate of this decomposition.

Phosphonium Chloride (3) from Betaine 4.—A solution of **4** (0.50 g, 1.2 mmol) in methanol (10 ml) was saturated with gaseous HCl and then dried. The drying agent was removed by vacuum filtration and washed with several portions of methanol to dissolve the adhering gummy precipitate. Evaporation of the combined filtrate and washings, followed by trituration of the residue with ether, afforded 0.49 g (90%) of white crystals, mp 182–183.5°, which were identified as **3** by a mixture melting point determination and ir spectral comparisons.

Reactions of Betaine 4 with Aldehydes. A. Benzaldehyde.—A freshly prepared sample of **4** (6.32 g, 15.0 mmol) was added to a solution of benzaldehyde (1.59 g, 15.0 mmol) in benzene (60 ml), and the mixture was refluxed under nitrogen with stirring for 1.5 hr. Removal of solvent under vacuum, followed by vacuum fractionation of the residue, gave three fractions: (1) bp 75–126° (mostly 126°) at 0.75–0.95 mm, 2.70 g; (2) bp 176–178° (temperature possibly inaccurate owing to low distillation rate) at 1.0 mm, 2.54 g; and (3) bp *ca.* 215° at 0.75 mm, 0.75 g. Fraction 1 was shown to be mostly tri-*n*-butylphosphine oxide (crude yield, 83%) by the usual variety of spectral comparisons with authentic material. Similar comparisons indicated that fraction 2 was stilbenol **8** (yield, 55%) in essentially pure form. Crystallization of fraction 2 from methanol–water, followed by low-temperature recrystallization from a very small amount of ether, gave a sample of **8** melting at 92.5–93° (lit. mp 90–91°,[4] 91–93°[27]). Spectral data indicated that fraction 3 was a complex mixture.

B. *n*-Heptaldehyde.—Three reactions were carried out in dry benzene under nitrogen, using the following conditions (millimoles of aldehyde per millimole of **4**, milliliters benzene per millimole of **4**; temperature, °C; reaction time, hr): 1.0, 6, 25–30, 116.5; 1.0, 4, reflux, 46.2; 10.0, 10, 49–53, 6.1. The mass spectra of the crude product mixtures all showed a strong peak at *m/e* 316 (exact *m/e* from one run, 316.2763; calcd for $C_{22}H_{36}O$, 316.2766); this was shown to be a parent ion by comparative intensity measurements at low and high voltages (10 and 70 eV). The presence of this peak, together with peaks at *m/e* 301 (strong at 70 eV, presumably $C_{21}H_{36}O$) and 245 (medium at 70 eV, presumably $C_{17}H_{25}O$), suggested that the anticipated Wittig product, 2,6-di-*t*-butyl-4-(1-octen-1-yl)phenol, had been formed to some extent. Yet attempts to recover the pure phenol by fractional distillation under vaccum were not successful. Qualitative vpc, ir, and mass spectral analyses showed that the other Wittig product, tri-*n*-butylphosphine oxide, had been formed in all of these experiments. A minor amount of a second liquid phase (apparently water) was formed in the reactions run at elevated temperatures. The reaction run at 25–30° yielded a small amount of 3,5-di-*t*-butyl-4-hydroxybenzaldehyde, which was isolated and identified by an nmr spectral comparison *vs.* authentic material.

***trans*-3,5-Di-*t*-butyl-4-stilbenol (8) from Quinone Methide 2, Tri-*n*-butylphosphine, and Benzaldehyde.**—A solution of tri-*n*-butylphosphine (16.21 g, 80.1 mmol) and benzaldehyde (9.29 g, 87.5 mmol) in benzene (80 ml) was warmed to 50° and kept at 50 ± 1° while a freshly prepared solution of **2** [80.1 mmol, obtained in the usual way from 20.40 g (80.1 mmol) of **1** and 8.44 g (83.4 mmol) of triethylamine] in benzene (500 ml) was added dropwise with stirring under nitrogen during 1.0 hr. Stirring under nitrogen at 50 ± 1° was continued for an additional 6.5 hr, and the mixture was then allowed to stand at room temperature under nitrogen overnight. Following successive extractions with 5% hydrochloric acid (three 200-ml portions) and 2 *N* sodium carbonate (three 200-ml portions), the organic moiety was dried, concentrated under vacuum, and distilled to recover two major fractions: (1) bp 120–124° at 0.13–0.27 mm, 12.83 g; and (2) bp 171–178° at 0.25–0.33 mm, 15.32 g. Ir and nmr spectral comparisons showed that fraction 1 was tri-*n*-butylphosphine oxide (73%). Crystallization of fraction 2 from aqueous methanol afforded 14.32 g (58%) of stilbenol **8** in two crops: mp 93–94° (12.52 g) and 91–93° (1.80 g). Both crops gave an nmr spectrum that was identical with the spectrum of an authentic specimen.[4]

Decompositions of Betaine 4 in Aprotic Solvents.—Mixtures of the betaine and C_6D_6 were prepared in nmr sample tubes and thoroughly degassed by bubbling with nitrogen. The tubes were then stoppered tightly and warmed gently until homogeneous solutions were obtained. Immediate examination of these solutions by nmr showed that all of the betaine had decomposed, and that bisphenol **9** and tri-*n*-butylphosphine were the major decomposition products. These identifications were confirmed by peak enhancements resulting from the addition of authentic specimens. Minor peaks arising from one or more unidentified by-products appeared in the olefinic–aromatic regions of the spectra, and qualitative comparisons showed that by-product yields were lowest when freshly prepared samples of **4** were employed. Several reaction mixtures were analyzed quantitatively by programmed temperature vpc, using pure compounds for calibration and *n*-eicosane for internal standardization. In this way the yields of bisphenol **9** and tri-*n*-butylphosphine were found to be *ca.* 80 and 95–100%, respectively.

Decompositions of betaine **4** were also carried out in anhydrous *p*-dioxane, $C_6D_5CD_3$, or cyclohexene, using a procedure identical to that described above. For runs in cyclohexene, the solvent was evaporated under nitrogen and replaced by C_6D_6 prior to product analysis. Nmr measurements showed that bisphenol **9** and tri-*n*-butylphosphine were the major products of all of these reactions, and that by-products derived from the solvent were not formed in experiments where cyclohexene was employed. The cyclohexene results were confirmed by programmed temperature vpc and mass spectral analyses.

A solution of **4** in CD_3OD was allowed to stand at room temperature until the nmr spectrum showed that the benzylic protons had been completely replaced by deuterium. Most of the solvent was then evaporated under nitrogen, and the residue was taken to complete dryness under vacuum. After addition of C_6D_6, the deuterated betaine was decomposed in the usual way. The nmr spectrum of the decomposition products showed no peaks for the olefinic or hydroxyl protons of **9** but was otherwise identical with the spectra obtained previously.

2,4-Di-*t*-butyl-9-chlorospiro[5.5]undeca-1,4,8-trien-3-one (13).—This compound was obtained by reaction of chloroprene with quinone methide **2**. The procedure followed was similar to that described by McClure,[12] except that the quinone methide solution was prepared separately by our usual method[6] and then added to the diene. Recrystallization of the crude product from methanol and then from ethanol gave **13** as white needles: mp 110–111° (lit.[12] mp 111–112°); uv max (isooctane) 241 mμ (log ϵ 4.05) and 367 (1.32) [lit. uv max (isooctane)[12] 242 mμ (log ϵ 3.96), uv max (solvent not specified)[28] 241 mμ (log ϵ 3.93) and 363 (1.28)]; nmr (CCl_4) δ 6.49 (s, 2, 1- and 5-CH), 5.74–5.91 (m, 1, 8-CH), 2.29–2.56 (m, 2, 10-CH_2), 2.05–2.21 (m, 2, 7-CH_2), 1.71 (t, 2, J = 6.4 Hz, 11-CH_2), and 1.22 ppm (s, 18, 2 *t*-Bu). The nmr spectrum seems inconsistent with a possible alternative structure, *viz.*, the 8-chloro isomer of **13**. The 8-chloro formulation would appear to require coupling of the 1.71

(25) C. D. Cook, *J. Org. Chem.*, **18**, 261 (1953).

(26) *Cf.* ref 7, pp 63, 64, and 74, and references cited therein; S. O. Grim and J. H. Ambrus, *ibid.*, **33**, 2993 (1968).

(27) H.-D. Becker, *ibid.*, **34**, 1211 (1969).

(28) W. R. Hatchard, *J. Amer. Chem. Soc.*, **80**, 3640 (1958).

δ triplet with the δ 2.05–2.21 multiplet, whereas inspection of the latter band immediately shows that it is not broad enough to incorporate a triplet with J = 6.4 Hz (the width reported for the multiplet is that of the total absorption envelope, rather than the separation of the two outermost maxima). McClure's hypothesis[12] concerning the structure of **13** is thus considered to be correct.

Decomposition of Betaine 4 in the Presence of Chloroprene.—A solution of chloroprene (8.85 g, 100 mmol) in dry benzene (10 ml) was degassed by bubbling with nitrogen. Betaine **4** (0.42 g, 1.0 mmol) was then added, and the mixture was stirred under nitrogen at 50 ± 1° for 1.0 hr. After cooling to room temperature, the mixture was extracted with 5% hydrochloric acid (two 50-ml portions), washed with 5% sodium bicarbonate solution (two 50-ml portions), dried, and evaporated under vacuum. An nmr spectrum showed that the composition of the residue (0.21 g) was complex; however, the presence of an appreciable amount of trienone **13** was clearly revealed by the appearance of peaks previously assigned (*vide supra*) to the 1- and 5-CH, 8-CH, 7-CH_2, 11-CH_2, and *t*-butyl groups of this compound (the 10-CH_2 multiplet was obscured by resonances from other products). These peaks had the correct multiplicities and relative intensities, and their origin was confirmed by intensity enhancements resulting from the addition of authentic **13**. A rough analysis of the residue by programmed temperature vpc indicated the presence of bisphenol **9** (evidently the major constituent), trienone **13**, bisphenol **14**, and unidentified compounds. Compounds **9**, **13**, and **14** were identified by retention times and, in the case of **14**, by comparing the ir and nmr spectra of a trapped fraction with the spectra of an authentic specimen.[29]

***p*-Methoxybenzyltri-*n*-butylphosphonium Chloride (16).**—Tri-*n*-butylphosphine (10.12 g, 50.0 mmol) was added under nitrogen during 5 min to a stirred solution of *p*-methoxybenzyl chloride[30] (7.83 g, 50.0 mmol) in dry benzene (25 ml). The nitrogen-blanketed mixture was then stirred at reflux temperature for 3.1 hr, kept at room temperature for an additional 6.7 hr, and evaporated under vacuum to give a solid residue which was suspended in ether, filtered with suction, and washed thoroughly on the filter with several fresh portions of ether. Drying of the solid under vacuum at 60° gave 17.11 g (95%) of pure **16** as white microcrystals: mp 105–106.5°; nmr ($CDCl_3$) δ 6.8–7.5 (AA'BB' portion of AA'BB'X m where X is phosphorus, 4, by computer calculation,[31] $J_{AA'}$ = 2.5, $J_{BB'}$ = 2.5, J_{AB} = $J_{A'B'}$ = 8.9, $J_{AB'}$ = $J_{A'B}$ = 0.1, J_{AX} = $J_{A'X}$ = 2.0, J_{BX} = $J_{B'X}$ = 0.0 Hz; aromatic H), 4.22 (d, 2, J = 15 Hz, CH_2Ar), 3.79 (s, 3, CH_3O), 2.2–2.6 (m, 6, 3 CH_2Pr), 1.2–1.7 (m, 12, 3 $CH_2CH_2CH_3$), and 0.92 ppm (highly distorted t, 9, $J \cong$ 6 Hz, 3 CH_2CH_3); for uv spectrum, see Table I.

Anal. Calcd for $C_{20}H_{36}ClOP$: C, 66.93; H, 10.11; Cl, 9.88; P, 8.63. Found: C, 66.96; H, 10.09; Cl, 10.07; P, 8.67.

Attempted Reaction of *p*-Methoxybenzylidenetri-*n*-butylphosphorane (15) with Phosphonium Chloride (16).—A solution of **16** (1.80 g, 5.01 mmol) in dry benzene (15 ml) was thoroughly degassed by the freeze–thaw method and blanketed with nitrogen. *n*-Butyllithium in hexane (1.55 ml of 15.20% solution, 2.50 mmol) was then added through a rubber septum by means of a hypodermic syringe, and the mixture was stirred under nitrogen at 50 ± 1° for 16.4 hr. After saturation with dry HCl, the mixture was filtered to remove a small amount of infusible white solid (very hygroscopic, presumably LiCl), which was quickly washed with several fresh portions of benzene. Evaporation of the combined filtrate and washings yielded a colorless, semicrystalline residue (1.98 g, presumably contained some LiCl) whose only organic constituent was **16**, judging from the material's nmr spectrum.

Tri-*n*-butyl(α-phenyl-3,5-di-*t*-butyl-4-hydroxyphenethyl)phosphonium Chloride (19a).—*n*-Butyllithium (12.25 ml of a 15.20% solution in hexane, 19.8 mmol) was added under nitrogen to a well-stirred suspension of powdered benzyltri-*n*-butylphosphonium chloride[32] (6.60 g, 20.1 mmol) in dry benzene (75 ml). Stirring under nitrogen was continued for 2.0 hr; then a freshly prepared solution of quinone methide **2** [20.0 mmol, from 5.10 g (20.0 mmol) of phenol **1** and 2.11 g (20.9 mmol) of triethylamine] in dry *n*-heptane (90 ml) was added to the stirred mixture during 4 min. Following an additional 5 hr of stirring under nitrogen, the well-agitated mixture (now containing a reddish tar) was acidified by dropwise addition of 2.5 *M* hydrochloric acid (50 ml). During the acidification period (10 min) a white precipitate of **19a** appeared. After treatment of the mixture with 5 ml of concentrated hydrochloric acid and 10 more min of stirring, the precipitate was recovered by suction filtration and washed thoroughly with petroleum ether (bp 30–60°). The crude, air-dried product weighed 10.2 g (94%) and melted at 182–186°; upon recrystallization from benzene (with filtering to remove a small amount of insoluble material) it afforded 7.78 g (72%) of white crystals melting at 189–190.5°. A further recrystallization from benzene gave tiny, snow-white needles of pure **19a**: mp 189.5–191.5°; ir (CS_2) 3630 cm^{-1} (sharp and weak, hindered phenol OH); nmr ($CDCl_3$) δ 7.2–7.6 (m, 5, C_6H_5), 6.86 (s, 2, *meta* H of tetrasubstituted ring), 5.08 (s, 1, OH), 4.61 (overlapping dt appearing as a five-peak m, 1, J_{HP} = 15, J_{HH} = 8 Hz, $ArCH_2CHP$), 3.33 (distorted t, 2, $J_{HP} \cong J_{HH} \cong$ 8 Hz, $ArCH_2CHP$), 2.2–2.7 (m, 6, 3 CH_2Pr), 1.2–1.6 (m with strong s at 1.34 ppm, 30, 3 $CH_2CH_2CH_3$ and 2 *t*-Bu), and 0.91 ppm (highly distorted t, 9, $J \cong$ 6 Hz, 3 CH_2CH_3).

Anal. Calcd for $C_{34}H_{56}ClOP$: C, 74.62; H, 10.32; Cl, 6.48; P, 5.66. Found: C, 74.49; H, 10.36; Cl, 6.57; P, 5.62.

In a similar experiment, the quinone methide solution was added during 20 min, and the mixture was acidified 15 min after the addition was complete. The crude product (**19a**) was recovered in quantitative yield; it melted at 179–181° and contained only traces of impurities detectable by nmr analysis.

Attempted Decompositions of Betaines 18a and 18b.—A solution of betaine **18a** was obtained in the manner described above by rapid addition of a solution of quinone methide **2** [from 2.55 g (10.0 mmol) of phenol **1** and 1.06 g (10.5 mmol) of triethylamine] in dry benzene (60 ml) to a solution of ylide **17** [from 6.21 ml (10.0 mmol) of 15.20% *n*-butyllithium in hexane and 3.30 g (10.0 mmol) of benzyltri-*n*-butylphosphonium chloride] in dry benzene (40 ml). The mixture was refluxed vigorously with stirring under nitrogen for 5.0 hr, then cooled to room temperature, and saturated with gaseous HCl. After filtering with suction to remove a white solid (infusible and hygroscopic, evidently LiCl, 0.45 g, 106%), the solution was reduced by boiling to a volume of *ca.* 30–40 ml, cooled to room temperature, and diluted with petroleum ether (*ca.* 75 ml, bp 30–60°). The precipitate was recovered by vacuum filtration and washed repeatedly with petroleum ether; it weighed 4.86 g and was shown by nmr analysis to be essentially pure **19a** (yield, 89%) containing no detectable amount of stilbenol **8**. Evaporation of the combined filtrate and washings yielded 0.44 g of pale brown, very viscous oil containing **19a** (50–75 mol %) and unidentified compounds, but very little (if any) of **8** (analysis by nmr).

n-Butyllithium (0.62 ml of a 15.20% solution in hexane, 1.0 mmol) was added to a nitrogen-flushed suspension of phosphonium chloride **19a** (1.09 g, 1.99 mmol) in dry benzene (20 ml). The mixture was refluxed under nitrogen with stirring for 17.8 hr, cooled to room temperature, acidified with gaseous HCl, and then filtered with suction to remove LiCl. The LiCl was washed repeatedly with benzene, and the combined filtrate and washings were evaporated under vacuum. Nmr analysis showed that the solid residue was essentially pure **19a** (1.10 g, 101%); no trace of **8** could be detected.

A solution of phosphonium chloride **16** (3.59 g, 10.0 mmol) in dry benzene (40 ml) was degassed by bubbling with nitrogen and then treated with *n*-butyllithium in hexane (6.21 ml of 15.20% solution, 10.0 mmol). The mixture was stirred under nitrogen for 2.1 hr, combined with a freshly prepared solution of quinone methide **2** [from 2.55 g (10.0 mmol) of phenol **1** and 1.06 g (10.5 mmol) of triethylamine] in dry benzene (60 ml), and refluxed vigorously with stirring under nitrogen for 92.5 hr. Acidification with anhydrous HCl, followed by suction filtration, washing of the recovered LiCl with dry benzene, and evaporation under vacuum of the combined filtrate and washings afforded a semisolid residue which was shown to be mostly the phosphonium chloride **19b** (6.21 g, crude yield 108%) by nmr analysis ($CDCl_3$): δ 7.27–7.49 (AA' portion of AA'BB'X m having X = phosphorus, 2, aromatic H *meta* to CH_3O), 6.80–7.02 (BB' portion of the AA'BB'X m overlapping with s at 6.86 ppm, 4, aromatic H *ortho* to CH_3O, aromatic H *meta* to OH), 5.38 (broad s, 1, OH), 4.45 (overlapping dt appearing as a five-peak m, 1, J_{HP} = 15, J_{HH} = 8 Hz, $ArCH_2CHP$), 3.80 (s, 3, CH_3O), 3.29 (distorted t, 2, $J_{HP} \cong J_{HH} \cong$ 8 Hz,

(29) C. R. Bohn and T. W. Campbell, *J. Org. Chem.*, **22**, 458 (1957).

(30) J. Lee, A. Ziering, L. Berger, and S. D. Heineman, *Jubilee Vol. Dedicated Emil Christoph Barell*, 264 (1946); *Chem. Abstr.*, **41**, 6246 (1947).

(31) We are indebted to Dr. J. J. R. Reed for performing this computation.

(32) G. Witschard and C. E. Griffin, *J. Chem. Eng. Data*, **9**, 255 (1964).

$ArCH_2CHP$), 2.2–2.6 (m, 6, 3 CH_2Pr), 1.2–1.7 (m with intense s at 1.34 ppm, 30, 3 $CH_2CH_2CH_3$ and 2 *t*-Bu), and 0.91 ppm (highly distorted t, 9, $J \cong 6$ Hz, 3 CH_2CH_3).

Reaction of Phosphonium Chloride (3) with *n*-Butyllithium.—*n*-Butyllithium solution (15.20% in hexane, 1.24 ml, 2.00 mmol) was added to a mixture of **3** (0.914 g, 2.00 mmol) and dry benzene (20 ml) that had previously been degassed by the freeze–thaw method and blanketed with nitrogen. After 2.0 hr of stirring at room temperature, the mixture was stirred for 1.0 hr under vigorous reflux, cooled (all operations described thus far were performed under nitrogen), saturated with anhydrous HCl, and filtered with suction. The precipitate (an infusible, hygroscopic white powder: presumably LiCl) was washed with several small portions of benzene, and the combined filtrate and washings were evaporated under vacuum. Nmr analysis showed that bisphenol **9** (yield, 55–65%) and phosphonium chloride **3** (recovery, 30–40%) were major constituents of the semisolid residue (0.95 g). These identifications were confirmed by peak enhancements produced by the addition of authentic specimens, and the presence of **9** was also indicated by vpc and mass spectral analysis.

***trans*-3,5-Di-*t*-butyl-4-stilbenol (8) from 4-Benzylmethylene-2,6-di-*t*-butyl-2,5-cyclohexadien-1-one (20).**—A solution of quinone methide **20** (0.31 g, 1.0 mmol) in dry benzene (5 ml) was degassed by bubbling with nitrogen. Tri-*n*-butylphosphine (0.20 g, 1.0 mmol) was then added with stirring, and the solution was allowed to stand at room temperature for 3.3 hr. Evaporation under vaccum left an oily residue that solidified when scratched. Drying of the solid on a porous plate gave snow-white microcrystals, mp 89.5–90°, which were shown to be essentially pure **8** by a mixture melting point determination and nmr analysis.

A solution of quinone methide **20** (0.073 *M*) and tri-*n*-butylphosphine (0.160 *M*) in C_6D_6 was examined by nmr 2–3 min after preparation. The spectrum showed that **20** had undergone quantitative conversion to **8** during the brief reaction period.

Registry No.—Tributylphosphine, 998-40-3; **2**, 2607-52-5; **3**, 24164-84-9; **4**, 24164-85-0; **8**, 21449-69-4; **13**, 24164-86-1; **16**, 24164-87-2; **19a**, 24164-88-3; **19b**, 24164-89-4.

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Diels–Alder Adducts of Acetoxy-1,3-dienes and *p*-Benzoquinone

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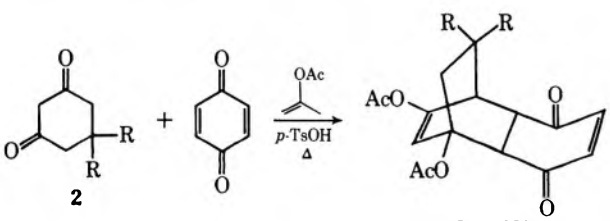
Cyclic acetoxy-1,3-dienes, generated *in situ* from 1,3-cyclohexanediones or isophorone, undergo Diels–Alder reaction with *p*-benzoquinone to afford 5,8-ethano-4a,5,8,8a-tetrahydro-1,4-naphthoquinone derivatives. The hydrolysis, aromatization, and Grob fragmentation of these derivatives are discussed.

The first paper[2] in this series described the *in situ* generation of acetoxy-1,3-dienes by the reaction of isopropenyl acetate with a variety of cyclic enones and diones, and their reaction with maleic anhydride. We now report the reaction of these acetoxy-1,3-dienes with *p*-benzoquinone and describe the hydrolysis products obtained from the resulting adducts.

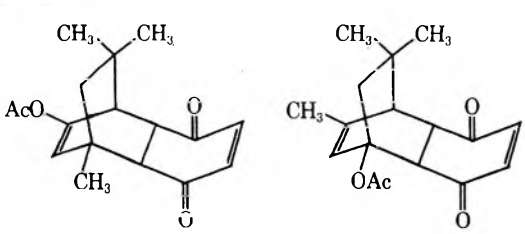
When dimedone (**2**, R = CH_3) or 1,3-cyclohexanedione is heated with an equivalent amount of *p*-benzoquinone in isopropenyl acetate containing a catalytic amount of *p*-toluenesulfonic acid, crystalline adducts **1** and **3** are obtained in about 55% yield.



2

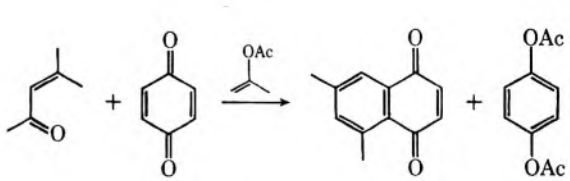
1, R = CH_3
3, R = H

Isophorone, which gives two different enol acetates, similarly afforded a mixture of adducts **4** and **5** in a 42:58 ratio.



4 **5**

Attempts to condense *p*-benzoquinone with other conjugated carbonyl compounds such as crotonaldehyde, tiglaldehyde, and 2-cyclopentylidene-cyclopentanone[3] gave tars and no recognizable products other than hydroquinone diacetate. Mesityl oxide also gave a complicated mixture from which 4,7-dimethyl-1,4-naphthoquinone (14%) and hydroquinone diacetate (43%) were isolated. The naphthoquinone probably arises by elimination of acetic acid and dehydrogenation of the 1:1 adduct produced from 4-acetoxy-2-methyl-1,3-pentadiene.



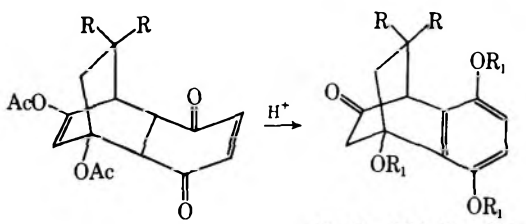
The isolation of adducts **1**, **3**, **4**, and **5** is surprising in view of the powerful enol acetylating conditions employed in this Diels–Alder condensation. The failure to induce aromatization may in part be attributed to the inherent strain of the bicyclo[2.2.2]octadiene system which would be produced since treatment of **1** and **3** with aqueous acid resulted in hydrolysis of both acetate groups and aromatization to give ketoquinols **6a**

(1) David Ross Fellow, 1968–1969.

(2) C. M. Cimarusti and J. Wolinsky, *J. Amer. Chem. Soc.*, **90**, 113 (1968).

(3) This conjugated ketone reacts readily with maleic anhydride under the conditions of this Diels–Alder reaction to give a 1:2 adduct, which will be described in a forthcoming publication.

and **6b**, which are readily characterized as triacetate derivatives **7a** and **7b**. Adduct **4** behaves in a similar fashion.



1 or **3**

6a, R = CH_3; R_1 = CH_3
b, R = R_1 = H
7a, R = CH_3; R_1 = Ac
b, R = H; R_1 = Ac

Base-catalyzed aromatization, on the other hand, proceeds rapidly; **1**, **3**, and **5** are transformed into **6a**, **6b**, and **8**, respectively, by brief heating with aqueous sodium bicarbonate solution. Aromatization of **3** with triethylamine in benzene followed by acetylation gave triacetate **7b**.

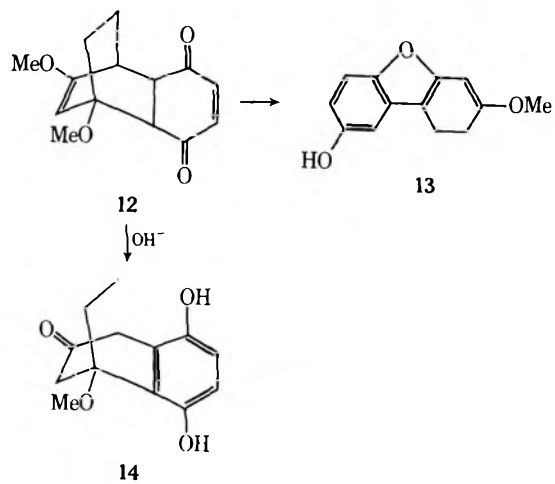
By contrast, acid hydrolysis of **5** proceeds slowly and after acetylation affords a mixture of **8a**, **9**, and **10**, Scheme I. **8a** and **9** crystallize together from the reaction mixture and analysis of their nmr spectra indicates the presence of 25% **8a**. Column chromatography permits the isolation of **9** (50%) and **10** (25%) in pure form.

Structural assignments for these compounds were based on their spectral properties. Triacetate **9** displayed a molecular ion at *m/e* 372 and infrared absorption at 11.22 μ characteristic of a terminal methylene group. A broad nmr doublet at 4.82 ppm integrating for two protons confirmed the presence of this group.

Diacetate **10**, an oil, displayed absorption at 5.68 and 6.0 μ indicative of aromatic acetate and α,β-unsaturated carbonyl groups. The molecular ion at *m/e* 330 and the nmr spectrum showing three aromatic protons centered at 7.0, a single vinyl hydrogen at 6.1, a singlet benzylic proton at 3.43, two acetate resonances at 2.35 and 2.25, and a vinyl methyl resonance at 1.79 ppm confirm the structural assignment **10**.

The formation of **10** undoubtedly involves a Grob type of fragmentation[4] of an intermediate hydroxyenedione **11** as pictured in Scheme I.

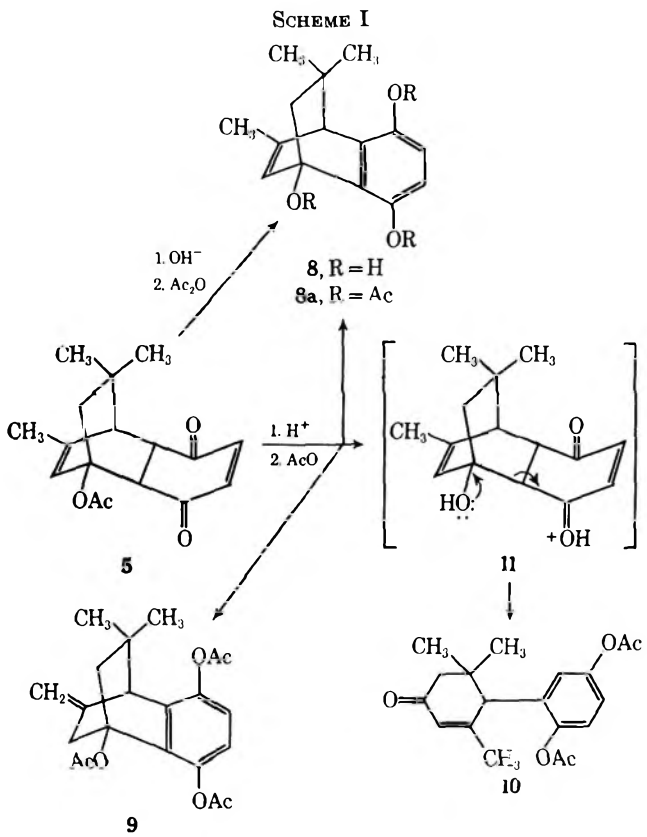
Birch and coworkers[5] have observed a facile Grob fragmentation of the methoxy derivative **12** on treatment with acid. We have confirmed that **12** is converted into vinyl ether **13** under conditions as mild as heating in aqueous methanol. Compound **12** even undergoes a Grob fragmentation on standing in deuteriochloroform. In basic media Birch[5] found that **12** is converted into ketoquinol **14**, with the hydrolysis of the vinyl ether most likely occurring during the acid workup. The quinols **14**, **8**, **6a**, and **6b** have not been observed to undergo Grob fragmentation in acid media.



12 **13** **14**

In conclusion it is seen that the hydrolysis of 5,8-ethanotetrahydro-1,4-naphthoquinone derivatives depends upon the nature of the bridgehead substituent and on the use of acidic or basic conditions. Basic conditions rapidly aromatizes these adducts yielding the corresponding quinols.[6] Aromatization is much slower under acidic conditions and appears to be especially slow when a double bond is present in the bicyclic ring system. The presence of a bridgehead methoxy group induces a facile Grob-type fragmentation. This is attributed[5] to the ability of a methoxy group to stabilize the incipient positive charge which develops during the fragmentation reaction. Grob fragmentation does not compete favorably with aromatization when the bridgehead substituent is acetoxy, but may do so when it is hydroxy.

SCHEME I



Experimental Section[7]

1,3-Diacetoxy-10,10-dimethyl-1,4,4a,8a-tetrahydro-1,4-ethanonaphthalene-5,8-dione (**1**).—A solution of 7.0 g of dimedone and

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

(5) A. J. Birch, D. N. Butler, and J. B. Siddall, *J. Chem. Soc.*, 2932, 2944 (1964).

(6) The conversion of thebainequinone to the thebainequinol appears to fall in this category; *cf.* K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1720 (1958), and references cited therein.

(7) All melting points are uncorrected. Infrared spectra were measured with a Perkin-Elmer Infracord spectrometer. Nmr spectra were determined with a Varian Associates A-60 spectrometer. The mass spectra were measured with a Hitachi RMU-6D mass spectrometer. The microanalyses were performed by Dr. C. S. Yeh and associates.

5.4 g of *p*-benzoquinone in 60 ml of isopropenyl acetate containing 25 mg of *p*-toluenesulfonic acid was refluxed for 40 hr. The volume was reduced to 30 ml under diminished pressure and the resulting solution was cooled to −20°. The solid, 8.13 g, was removed and recrystallized from hexane (Norit) to give pale yellow crystals: mp 121–123°; ir (Nujol) 5.65 (sh), 5.73, and 5.99 μ; nmr δ ($CDCl_3$) 0.98 (s, 3, CH_3), 1.18 (s, 3, CH_3), 1.42 and 2.41 (AB q, 2, J = 12.5 Hz, $-CH_2-$), 2.07 (s, 6, –OAc), 2.57 (m, 1), 3.32 (d of d, 1, J = 2.5 Hz, J = 9 Hz, C—H_{8a}), 3.87 (d, 1, J = 9 Hz, C—H_{4a}), 5.8 (d, 1, J = 2.0 Hz, –C=CH), 6.62 ppm (s, 2, CO—CH=CH—CO); mass spectrum (75 eV) *m/e* (relative intensity) 332 (0.15), 290 (17.5), 248 (16), 230 (10), 182 (19), 140 (35), 125 (40), 110 (12), 69 (15), 43 (100).

Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.10; H, 6.05.

Hydrolysis of 1.—A mixture of 370 mg of adduct **1** and 30 ml of 0.1 *N* hydrochloric acid was refluxed for 24 hr. The mixture was cooled and extracted with ether. The ether solution was washed with saturated salt solution and dried ($MgSO_4$). The ether was evaporated leaving an oil which was purified by thick layer chromatography using silica gel and ether to give 262 mg (96%) of liquid ketohydroxyquinol **6a**: ir (neat) 3.0 and 5.82 μ; nmr δ (CD_3CN) 0.74 (s, 3, CH_3), 1.1 (s, 3, CH_3), 1.92 (m, 2, $-C^9H_2$), 2.45 (d, 2, C^2H_2), 3.54 (s, 1, C^8H), 6.55 and 6.79 (AB q, 2, Ar—H), 6.1, 7.76, 8.94 ppm (s's, 3, –OH).

Quinol **6a** was dissolved in 1 ml of acetic anhydride and 2 ml of pyridine and kept at ambient temperature for 24 hr. The excess reagents were evaporated under diminished pressure and the resulting oil was dissolved in ether and the solution washed with saturated salt solution and dried ($MgSO_4$). The ether was removed and the resulting solid recrystallized from benzene–pentane to give 200 mg of triacetate **7a**: mp 161–162°; ir (Nujol) 5.66 and 5.75 μ; nmr δ ($CDCl_3$) 0.74 (s, 3, CH_3), 1.19 (s, 3, CH_3), 2.11, 2.26, 2.28 (s's, 9, –OAc), ~2.1 (m, 2, $-CH_2$), 2.91 (d, 2, C^2H_2), 3.38 (s, 1, C^4H), 6.88 and 7.1 ppm (AB q, 2, J = 9 Hz, Ar—H).

Anal. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.14; H, 5.67.

1,3-Diacetoxy-1,4,4a,8a-tetrahydro-1,4-ethanonaphthalene-5,8-dione (3).—The reaction of 8.8 g of 1,3-cyclohexanedione and 8.5 g of *p*-benzoquinone was carried out as described above and gave 10 g (58%) of adduct **3**. Several recrystallizations from ethyl acetate–hexane gave an analytical sample: mp 114–115.5°; ir (Nujol) 5.7 and 6.0 μ; nmr δ ($CDCl_3$) 2.08 (s, 6, OAc) and 5.79 ppm (d, 1, J = 1.8 Hz, –C=CH); mass spectrum (75 eV) *m/e* (relative intensity) 304 (1.5), 262 (55), 220 (72), 192 (25), 162 (22), 154 (57), 112 (88), 82 (28), 43 (100).

Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.92; H, 5.38.

Hydrolysis of Adduct 3. A. Acidic Conditions.—A mixture of 1.0 g of **3** and 40 ml of 0.1 *N* hydrochloric acid was refluxed for 100 min, cooled, saturated with salt, and extracted with ether. After drying, the ether was evaporated to give 750 mg of ketohydroxyquinol **6b**: ir 3.06 and 5.82 μ; nmr [$(CD_3)_2SO$] 6.5 and 6.7 ppm (AB q, 2, J = 9 Hz, Ar—H).

Hydrolysis of **3** with ethanolic hydrochloric acid gave the same quinol **6b**.

The triacetate **7b** was obtained by treatment with acetic anhydride and pyridine and after recrystallization from benzene–pentane exhibited mp 157–158°.

Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.27; H, 5.05.

B. Basic Conditions.—Adduct **3** (1.0 g) was heated with sodium bicarbonate in aqueous methanol for 15 min. Work-up gave a product whose nmr spectrum showed the absence of acetate methyl signals. Acetylation of the crude hydrolysis product afforded 600 mg of a crystalline solid, mp 157–158°, which was identical with the triacetate obtained by acid hydrolysis of **3**.

3-Acetoxy-1,10,10-trimethyl-1,4,4a,8a-tetrahydro-1,4-ethanonaphthalene-5,8-dione (4) and 1-Acetoxy-3,10,10-trimethyl-1,4,4a,8a-tetrahydro-1,4-ethanonaphthalene-5,8-dione (5).—The condensation of 25.6 g of isophorone with 20 g of *p*-benzoquinone gave a first crop of 10 g of adduct **5**. An analytical sample of **5** was obtained by sublimation *in vacuo* and displayed mp 119–121°; ir (Nujol) 5.74 and 6.0 μ; nmr 0.9 and 1.18 (s's, 6, CH_3—C—CH_3), 1.7 (d, 3, J = 1.5 Hz, CH_3C=C), 2.1 (s, 3, OAc), and 6.64 ppm (s, 2, CO—CH=CH—CO); mass spectrum (75 eV) *m/e* (relative intensity) 288 (9), 246 (10), 190 (20), 180 (48), 139 (18), 136 (20), 123 (42), 109 (31), 108 (39), 91 (16), 82 (86), 79 (17), 77 (22), 54 (28), 43 (100).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.88; H, 6.90.

The mother liquor obtained from the crystallization of **5** was saturated with pentane and cooled to −20° overnight to give 17.5 g of solid. Concentration and cooling gave a second crop of 6.5 g. Nmr analysis of these solids indicated the presence of adduct **4** contaminated by *ca.* 17% of **5**. A sublimed sample of **4** showed mp 68–72°; ir 5.7 and 6.0 μ; nmr ($CDCl_3$) 0.98 and 1.12 (s's, 6, CH_3—C—CH_3), 1.19 (s, 3, CH_3), 2.06 (s, 3, OAc), 2.68 (m, 2, $-CH_2-$), 3.35 (d of d, J = 9 Hz, J = 3 Hz, CH), 5.5 (d, 1, J = 2 Hz, H—C=C), and 6.61 ppm (s, 2, CO—CH=CH—CO); mass spectrum (75 eV) *m/e* (relative intensity) 288 (14), 273 (11), 246 (24), 231 (32), 228 (25) 213 (7), 190 (11), 180 (19), 138 (58), 137 (15), 124 (13) 123 (100), 91 (10), 82 (32), 43 (25).

Hydrolysis of 4.—A solution of 3.71 g of **4** in 40 ml of 50% aqueous methanol containing a few milliliters of concentrated hydrochloric acid was refluxed for 24 hr. Work-up gave an oil whose nmr spectrum showed the absence of acetate methyl signals. Treatment with acetic anhydride–pyridine yielded 1 g of a ketoquinol diacetate derivative which was recrystallized from benzene–hexane and exhibited mp 141–142°.

Anal. Calcd for $C_{19}H_{22}O_6$: C, 69.07; H, 6.77. Found: C, 69.07; H, 6.71.

Hydrolysis of 5. A. Acidic Conditions.—A solution of 2.50 g of **5** in 50 ml of ethanol containing 0.5 ml concentrated hydrochloric acid was refluxed for 72 hr. The solution was concentrated to a volume of 30 ml, and 200 ml of ice water was added. The mixture was extracted with ether and the ether solution was washed with dilute sodium bicarbonate solution and saturated brine solution. The ether solution was dried and evaporated leaving an oil which was taken up in 20 ml of acetic anhydride and 10 ml of pyridine. The solution was kept at ambient temperature for 30 hr. The usual work-up gave 1.75 g of white solid and 1.13 g of oil. Nmr analysis of the solid indicated it was comprised of 40% **8a** and 60% **9**. The oil showed two components on tlc (silica gel). Chromatography of the oil on silica gel and elution with hexane–ether gave **10**, while elution with hexane–ethyl acetate gave **9**.

A sample of **9** was recrystallized from benzene and showed mp 116–117°; ir ($CHCl_3$) 5.67 and 11.22 μ; nmr ($CDCl_3$) 0.68 and 1.13 (s's, 6, CH_3—C—CH_3), 2.11, 2.22, and 2.29 (s's, 9, –OAc), 4.82 (broad d, 2, C=CH_2), 6.8 and 7.01 ppm (AB q, 2, Ar—H); mass spectrum *m/e* (relative intensity) 372 (38), 368 (8.2), 330 (18), 316 (17), 274 (13), 232 (42), 190 (30), 43 (100).

Quinol diacetate **10** showed ir ($CHCl_3$) 5.68 and 6.0 μ; nmr ($CDCl_3$) 0.78 and 1.15 (s's, 6, CH_3—C—CH_3), 1.79 (d, 3, J = 1 Hz, CH_3C=C), 2.12 (s, 2, $-CH_2-$), 2.25 and 2.35 (s's, 6, –OAc), 3.43 (s, 1, Ar—CH–), 6.1 (s, 1, C=CH), 7.0 ppm (ABC m, 3, Ar—H); mass spectrum (75 eV) *m/e* (relative intensity) 330 (15), 288 (37), 272 (15), 246 (58), 232 (10), 231 (52), 190 (25), 161 (14), 147 (12), 83 (44), 43 (100).

B. Basic Conditions.—A solution of 1.0 g of **5** in 15 ml of methanol and 15 ml of saturated sodium bicarbonate solution was refluxed for 15 min, cooled, and added to 100 ml of saturated salt solution. Extraction with ether, followed by washing the ether solution with 10% hydrochloric acid, and then evaporation of the ether gave an oil which showed no carbonyl absorption in the ir. The oil was dissolved in 15 ml of acetic anhydride and 7 ml of pyridine. The resulting solution was kept at ambient temperature for 17 hr and after removing the volatile reagents *in vacuo* and crystallization from benzene–hexane there was obtained 800 mg of a white solid, **8a**: mp 166.5–167.5°; nmr ($CDCl_3$) 0.61 and 1.05 (s's CH_3—C—CH_3), 1.87 (d, 3, J = 1.1 Hz, CH_3C=C), 2.15, 2.21, and 2.28 (s's, 9 OAc), 6.1 (broad s, 1, C=CH), 6.66 and 6.88 ppm (AB q, 2, J = 9 Hz, Ar—H); mass spectrum (75 eV) *m/e* (relative intensity) 372 (<1), 316 (14), 274 (18), 232 (22), 190 (29), 111 (61), 97 (85) 95 (72), 71 (82), 55 (100), 43 (100).

Reaction of Mesityl Oxide and *p*-Benzoquinone.—The reaction of 3.0 g of mesityl oxide and 3.3 g of *p*-benzoquinone was conducted in the usual manner and afforded 6.0 g of solid which showed several components on tlc. Chromatography of 1.0 g of this solid on silica gel gave 140 mg of 5,7-dimethyl-1,4-naphthoquinone, mp 124–126° (lit.[8] mp 128–129°), 426 mg of 1,4-diacetoxybenzene, and 434 mg of unidentified tars.

(8) H. V. Euler and H. Hasselquist, *Ark. Kemi*, **2**, 367 (1950).

Registry No.—*p*-Benzoquinone, 106-51-4; **1**, 24097-79-8; **3**, 24097-80-1; **4**, 24097-81-2; ketoquinol diacetate derivative of **4**, 24097-82-3; **5**, 24097-83-4; **6a**, 24215-68-7; **6b**, 24097-84-5; **7a**, 24097-85-6; **7b**, 24097-86-7; **8a**, 24097-87-8; **9**, 24097-88-9; **10**, 24097-89-0.

Halomethyl Metal Compounds. XXXII. Insertion of Phenyl(bromodichloromethyl)mercury-Derived Dichlorocarbene into Carbon–Hydrogen Bonds. Alkanes and Alkylbenzenes[1]

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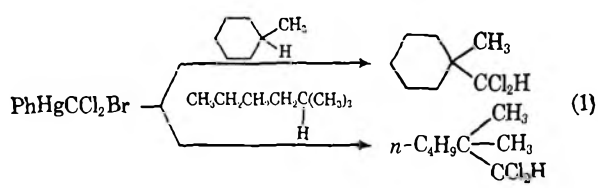
Received October 17, 1969

Phenyl(bromodichloromethyl)mercury has been found to insert CCl_2 into aliphatic C–H bonds. Most reactive in this reaction are tertiary C–H bonds; secondary C–H bonds are less reactive and no such insertion into methyl group C–H bonds was observed. The cases of 3-methylcyclohexene and *trans*-$Me_3SiCH{=}CHCHMe_2$ showed that a tertiary C–H bond can even compete for CCl_2 in some measure with a C=C bond. In the case of alkylbenzenes such as ethylbenzene and cumene, CCl_2 insertion occurred exclusively in the benzylic position. These reactions are of preparative utility. A mechanism involving a transition state (III) in which the carbon atom at which the C–H insertion is occurring bears a partial positive charge is suggested. The first case of an insertion of CBr_2 into a C–H bond (of ethylbenzene) is described.

The insertion of singlet state CH_2 into C–H bonds of of alkanes (→ C–CH_3 groups) is a well-known reaction,[6] but in 1962 an analogous insertion of a dihalocarbene into any kind of a C–H bond had not yet been encountered. During our early work on the CX_2 transfer reactions of phenyl(trihalomethyl)mercury compounds,[7] we sought to study the thermolysis of $PhHgCCl_2Br$ and $PhHgCCl_3$ in an inert medium. In view of the apparent lack of reactivity of CCl_2 derived from other sources toward C–H linkages, *n*-heptane was chosen as the "inert" medium. When phenyl(trichloromethyl)mercury was heated at reflux in *n*-heptane solution under nitrogen, phenylmercuric chloride precipitated (*ca.* 80% yield), and one of the volatile products obtained in very low yield upon work-up of the filtrate (glpc) was found by combustion analysis to have the empirical formula $C_8H_{16}Cl_2$, *i.e.*, (C_7H_{16} + CCl_2), an insertion product of CCl_2 into heptane. Because several isomeric (dichloromethyl)heptanes were possible, it was decided to study this novel reaction with a simpler substrate, cyclohexane. The decomposition of phenyl(bromodichloromethyl)mercury in refluxing cyclohexane during 3 hr gave phenylmercuric bromide (77%), tetrachloroethylene[8] (26%), cyclohexyl bromide (22%, based on available bromine), and a new compound identified by analysis and its nmr and ir spectra as (dichloromethyl)cyclohexane (32%). Dichlorocarbene insertion into a completely unactivated C–H bond in a preparatively useful yield was unprecedented and most surprising. Clearly, further studies were called for.

The unactivated secondary C–H bond is very low on the scale of reactivity toward CCl_2. Under the usual conditions which serve in the high yield dichlorocyclopropanation of olefins (3 mol of substrate to 1 mol of $PhHgCCl_2Br$ in benzene solution at 80°), the reaction of phenyl(bromodichloromethyl)mercury with cyclohexane proceeded very poorly, (dichloromethyl)cyclohexane being obtained in only trace yield. However, tertiary aliphatic C–H bonds were found to be more reactive. Thus, under these standard reaction conditions $PhHgCCl_2Br$ served to convert methylcyclohexane to 1-methyl-1-(dichloromethyl)cyclohexane in 15% yield and 2-methylhexane to 1,1-dichloro-2,2-dimethylhexane in 20% yield (eq 1). In neither case



(1)

was any insertion into CH_2 or CH_3 groups observed; insertion into the methine C–H appeared to be the exclusive process. These limited data suggest a reactivity sequence for aliphatic C–H bonds in the order tertiary C–H > secondary C–H > primary C–H. Indirect confirmation for this was provided in experiments with cyclohexene and 3-methylcyclohexene. In the case of the former, reaction with $PhHgCCl_2Br$ at 80° gave 7,7-dichloronorcarane as the sole product (eq 2),[9] but with 3-methylcyclohexene, where a tertiary C–H bond is available to compete with the C=C bond for CCl_2, both C=C addition and C–H insertion were

(1) (a) Part XXXI: D. Seyferth and K. V. Darragh, *J. Org. Chem.*, **70**, 1297 (1970). (b) preliminary communication: D. Seyferth and J. M. Burlitch, *J. Amer. Chem. Soc.*, **85**, 2667 (1963).

(2) National Institutes of Health Postdoctoral Fellow, 1964–1965.

(3) Postdoctoral Research Associate, on leave from the Department of Synthetic Chemistry, Faculty of Engineering, Kyôto University, 1968–1969.

(4) National Science Foundation Predoctoral Fellow, 1964–1966; Union Carbide Fellow, 1966–1967.

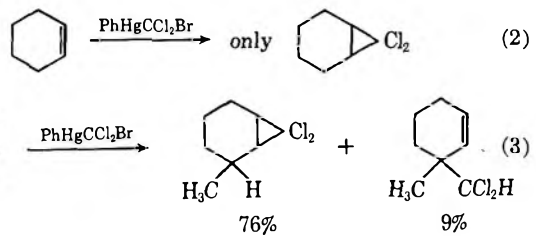
(5) Postdoctoral Research Associate, 1967–1968.

(6) (a) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, Chapter 2; (b) J. Hine, "Divalent Carbon," Ronald Press Co., New York, N. Y., 1964, Chapter 2; (c) D. F. Ring and B. S. Rabinovitch, *Can. J. Chem.*, **46**, 2435 (1968), and earlier references cited therein.

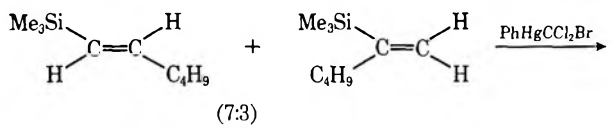
(7) First report: D. Seyferth, J. M. Burlitch, and J. K. Heeren, *J. Org. Chem.*, **27**, 1491 (1962).

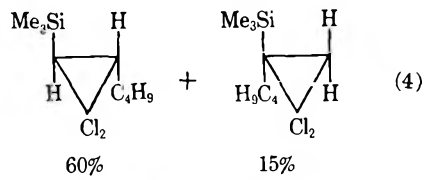
(8) Tetrachloroethylene is the product of decomposition of $PhHgCCl_2X$ (X = Cl or Br) in the absence of substrate capable of trapping dichlorocarbene and usually is found in low to moderate yield in reactions where the substrate is only poorly reactive toward CCl_2.[9]

(9) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J.-H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

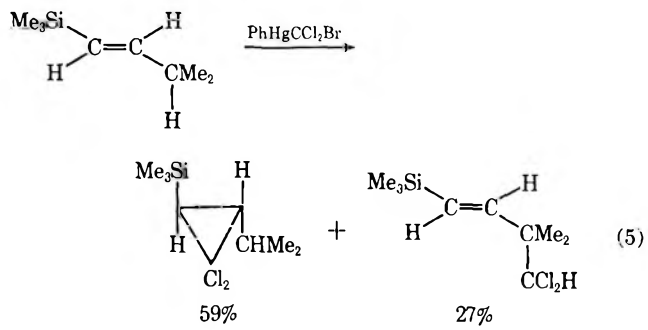


observed (eq 3).[10] A similar observation was made with vinylic silanes of the type $Me_3SiCH{=}CHR$. A mixture of *cis*- and *trans*-propenyltrimethylsilane gave only the expected C=C addition products,[9] as did a mixture of *trans*-$Me_3SiCH{=}CHC_4H_9$-*n* and $Me_3Si(n\text{-}C_4H_9){=}CH_2$ (eq 4). In contrast, the tertiary

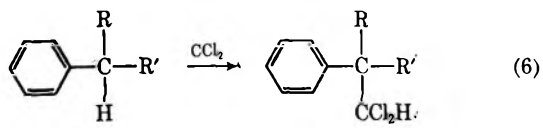




C–H bond of *trans*-$Me_3SiCH{=}CHCHMe_2$ competed effectively with the rather unreactive[12] Me_3Si-substituted C=C bond (eq 5). This tertiary C–H bond is also allylic and, hence, should be more reactive than that of 2-methylhexane.[9]



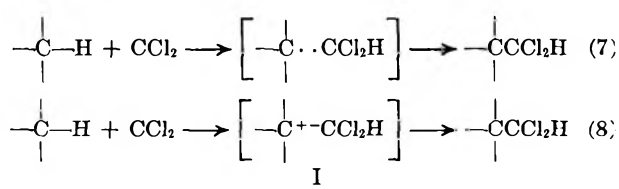
We were diverted from our intention of continuing studies of purely aliphatic systems by the report of Fields[13] that dichlorocarbene (generated *via* sodium trichloroacetate pyrolysis in 1,2-dimethoxyethane) inserted very specifically into benzylic C–H bonds of alkylbenzenes such as ethylbenzene, cumene, *p*-diisopropylbenzene, tetralin, and diphenylmethane (eq 6). The yields ranged from 17 to 39%. It was noteworthy



that only minute yields of such insertion products were obtained when the low-temperature $CHCl_3$–*t*-BuOK and CCl_3CO_2Et–NaOMe CCl_2-generating systems were used.[13] Fields commented that it appeared that the additional thermal energy associated with the sodium trichloroacetate procedure (80–85° reaction temperature) was an important factor and suggested that the CCl_2 insertion reaction mechanism may not be identical with the "normal" carbene insertion mechanism, *i.e.* that of CH_2 into C–H bonds.

It was, of course, of interest to study analogous reactions with phenyl(bromodichloromethyl)mercury for purposes of comparison, and we have carried out a brief investigation of the thermolysis of this mercurial in ethylbenzene and in cumene to see if results similar to those of Fields would be obtained. Such was the case, except that our yields of $PhCH(Me)CCl_2H$ and $PhCMe_2CCl_2H$, 35 and 58%, respectively, were approximately double those reported for the sodium trichloroacetate procedure. In the case of the reaction with cumene, two by-products, tetrachloroethylene (4%) and 1,1-dichloro-2-methyl-2-phenylcyclopropane (2%), were identified. Since the cumene used had been rigorously purified of olefins before use, the presence of the latter by-product may be indicative of a free-radical side reaction.[14] An example of the insertion of a CBr_2 moiety into a benzylic C–H linkage was provided by the decomposition of $PhHgCBr_3$ in ethylbenzene at 85°. β,β-Dibromoisopropylbenzene was obtained in 6.5% yield. The low yield probably is not a good indication of the efficiency of the reaction since the isolation and purification of the unstable, high-boiling product proved to be difficult.[15]

We shall defer a more detailed discussion of the mechanism of the insertion of dichlorocarbene into C–H bonds until a later paper of this series. The reactivity sequence observed (tertiary C–H > secondary C–H ≫ primary C–H), as well as the activation by adjacent phenyl groups may be rationalized in terms of either a radical process (eq 7) or a polar process in which a significant partial positive charge is placed on the carbon atom into whose bond to hydrogen the CCl_2 insertion is taking place (eq 8 shows the ionic extreme). To date no evidence for the occurrence of



CCl_2 in the diradical triplet state has been reported, and in its well-developed chemistry there has been no indication of radical reactions; all of the reactions of CCl_2 are best rationalized in terms of a singlet configuration.[16] Thus a polar process such as that shown in its extreme ion pair form (I) in eq 8 would be more in agreement with the known reactivity of CCl_2. It is our

(10) Of interest in this connection is the finding by Kung and Bissinger[11] that the reaction of cyclohexene with CCl_2 generated by the pyrolysis of chloroform at 500–600° produced not only 7,7-dichloronorcarane (and toluene, the thermolysis product of the latter), but also 3-(dichloromethyl)-cyclohexene. Thus the C–H insertion chemistry of dichlorocarbene may depend heavily on thermal activation. Our discussion in this paper is restricted to reactions carried out at 80° or below.

(11) F. E. Kung and W. E. Bissinger, *J. Org. Chem.*, **29**, 2739 (1964).

(12) D. Seyferth and H. Dertouzos, *J. Organometal. Chem.*, **11**, 263 (1968).

(13) E. K. Fields, *J. Amer. Chem. Soc.*, **84**, 1744 (1962).

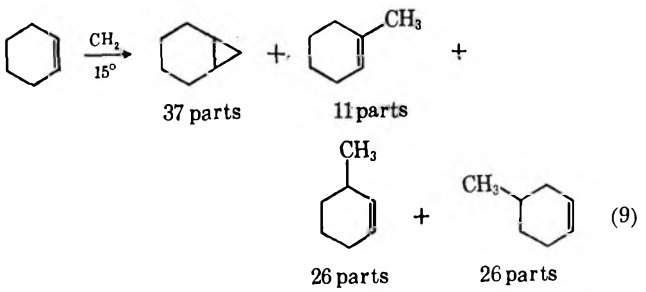
(14) It has been shown that α-methylstyrene (from which the observed cyclopropane must be derived) as well as bicumyl are produced in the irradiation of phenanthraquinone in cumene: R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 3405 (1953).

(15) Our recent report of the insertion of $PhHgCClBr_2$-derived CClBr into the benzylic C–H bond of cumene in 53% yield also should be noted: D. Seyferth, S. P. Hopper, and T. F. Jula, *J. Organometal. Chem.*, **17**, 193 (1969).

(16) Reference 6a, Chapter 8; ref 6b, Chapter 3.

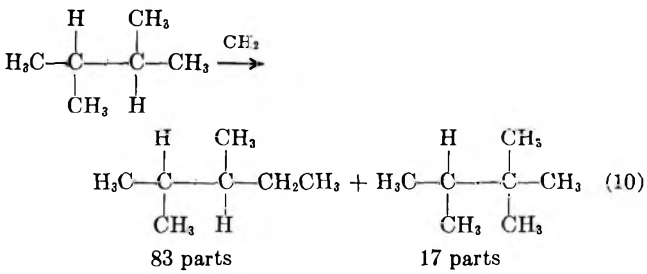
belief that the formation of by-products such as cyclohexyl bromide in the case of the $PhHgCCl_2Br$–cyclohexane reaction and 1,1-dichloro-1-methyl-1-phenylcyclopropane in the $PhHgCCl_2Br$–cumene reaction results from radical side reactions and that their formation is in no way indicative of the mechanism of the insertion of CCl_2 into the C–H bond.

In the reactions under discussion CCl_2 is much more selective than CH_2 in comparable reactions.[17,18] For instance, in the case of cyclohexene, CH_2 (from liquid phase CH_2N_2 photolysis) not only added to the C=C bond but also inserted into all possible C–H bonds (eq 9). With 2,3-dimethylbutane, CH_2 insertion ap-



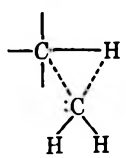
(9)

peared to be nearly random with respect to available primary and tertiary C–H bonds (eq 10). Subsequent



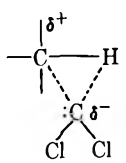
(10)

work by Doering and Prinzbach[19] suggested that such CH_2 insertion into C–H bonds involved a direct insertion process (transition state II). Our results with



II

CCl_2 are in marked contrast to those found with CH_2, and we believe that the selectivity of CCl_2 observed in these reactions is most reasonably accommodated by a transition state in which there is some development of charge (III). This transition state is analogous to



III

the one we suggested for CCl_2 insertion into the Si–H bond on the basis of the results of a previous study.[20]

(17) W. von E. Doering, R. G. Buttery, R. G. Laughlin, and N. Chaudhuri, *J. Amer. Chem. Soc.*, **78**, 3224 (1956).

(18) D. B. Richardson, M. C. Simmons, and I. Dvoretzky, *ibid.*, **82**, 5001 (1960); **83**, 1934 (1961).

(19) W. von E. Doering and H. Prinzbach, *Tetrahedron*, **6**, 24 (1959).

(20) D. Seyferth, R. Damrauer, J. Y.-P. Mui, and T. F. Jula, *J. Amer. Chem. Soc.*, **90**, 2944 (1968).

A crude estimate of the relative reactivity of an allylic tertiary C–H bond (*vs.* 1-heptene) can be obtained from the results shown in eq 5. Here the total yield of products was 86%, so that the relative yields of the two products obtained can serve, as a first approximation, as a measure of the relative reactivity of the C=C bond and the tertiary C–H bond in the reactant, *trans*-$Me_3SiCH{=}CHCHMe_2$. This value, $k(C{-}H)/k(C{=}C)$, is 0.46. The relative reactivity *vs.* 1-heptene of the unsubstituted vinyl group attached to silicon in the compound $Me_2EtSiCH{=}CH_2$ toward CCl_2 at 80° is 0.069;[21] so the relative reactivity of the tertiary C–H of *trans*-$Me_3SiCH{=}CHCHMe_2$ would be in the order of 0.03 on that scale. We are assuming that the trimethylsilyl group has no effect on the reactivity of the C–H bond in the γ position; this, however, may not be the case. It is thus understandable why essentially no C–H insertion chemistry is observed with CX_2 generating systems in which a trihalomethide ion source is treated with an alkali metal alkoxide. In such systems the side reactions occurring between the CX_2 and the reagent used in its generation (or the products derived therefrom) become the main processes when the substrate used as CX_2 trap is rather unreactive. The present study thus offers another example of the unique applicability of the phenyl(trihalomethyl)mercury reagents in the study of reactions of dihalocarbenes with poorly reactive substrates.

Experimental Section

General Comments.—All reactions were carried out under an atmosphere of prepurified nitrogen or argon. Infrared spectra were recorded using a Baird Model B or Perkin-Elmer Infracord 237 or 337 spectrophotometers. Nmr spectra were obtained using a Varian Associates A-60 or T-60 spectrometer. Chemical shifts are given in δ units, parts per million downfield from internal TMS. Thin layer chromatographic analysis of reaction mixtures for organomercury compounds was performed as described in a previous paper of this series.[22] Gas–liquid partition chromatography (glpc) was carried out using MIT isothermal units and F & M temperature-programmed gas chromatographs. The columns were packed with 25% General Electric Co. SE-30 silicone rubber gum on Johns Manville Chromosorb W or P, Dow Corning 710 silicone oil on Chromosorb P, or Dow Corning DC 200 silicone oil on Chromosorb P unless otherwise noted. The internal standard method was used in glpc yield determination.

Phenyl(bromodichloromethyl)mercury, phenyl(tribromomethyl)mercury, and phenyl(trichloromethyl)mercury were prepared as described by us previously;[22,23] the preferred procedure is that given in ref 23.

Preparation of Starting Organosilicon Olefins. (a) ***trans*-1-Trimethylsilyl-3-methyl-1-butene.**—A mixture of 6.12 g (0.09 mol) of 3-methyl-1-butyne (Farchan Research Laboratories), 9.0 ml (at −78°) (*ca.* 0.09 mol) of trimethylsilane, and 20 μl of a solution of chloroplatinic acid in 2-propanol (1 g in 5 ml) was sealed in a bomb tube under a nitrogen atmosphere and kept for 2 days at room temperature. The reaction mixture then was filtered from some black solid and distilled at reduced pressure to give 9.92 g (78%) of the monoaddition product [bp 56° (65 mm), $n^{25}D$ 1.4166; lit.[24] bp 124–125°, $n^{20}D$ 1.4180] as well as 0.6 g of material of bp *ca.* 40° (0.6 mm), presumably the diaddition product. Glpc analysis of the monoaddition product (General Electric Co. XF-1112 on Chromosorb W at 100°) showed that two components were present; the peak area ratios were 87:13. An nmr spectrum in CCl_4 of the monoaddition

(21) D. Seyferth and H. Dertouzos, *J. Organometal. Chem.*, **11**, 263 (1968).

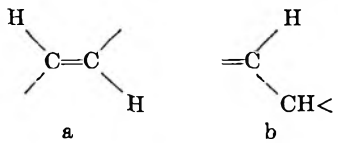
(22) D. Seyferth and J. M. Burlitch, *ibid.*, **4**, 127 (1965).

(23) D. Seyferth and R. L. Lambert, Jr., *ibid.*, **16**, 21 (1969).

(24) R. A. Benkeser, M. L. Burrous, L. E. Nelson, and J. V. Swisher, *J. Amer. Chem. Soc.*, **83**, 4385 (1961).

product confirmed this: two different Me_3Si resonances were observed at δ 0.10 and 0.15 ppm, with peak area ratio of 86:14. The pure components were isolated by preparative glpc.

The major component was *trans*-1-trimethylsilyl-3-methyl-1-butene: $n^{25}D$ 1.4156; nmr (neat) δ 6.30–5.41 [six lines, the AB part of an ABX spectrum, J (a) = 18 Hz, J (b) = 5 Hz], 2.33



a b

(1 H, Me_2CH–) m, 1.04 [6 H, $(CH_3)_2C$] d (J = 6.8 Hz), 0.10 ppm (9 H, Me_3Si) s.

Anal. Calcd for $C_8H_{18}Si$: C, 67.51; H, 12.75. Found: C, 67.27; H, 12.57.

The minor component was not obtained in analytical purity: nmr (neat) δ 5.71 (1 H, =CH *trans* to *i*-Pr) double d, 5.42 (1 H, =CH *cis* to *i*-Pr) d (J = 2.4 Hz), 2.49 (1 H, Me_2CH–) m, 1.08 [6 H, $(CH_3)_2C$] d (J = 7.0 Hz), 0.15 ppm (9 H, Me_3Si) s.

Anal. Calcd for $C_8H_{18}Si$: C, 67.51; H, 12.75. Found: C, 68.69; H, 12.96.

(b) **Hydrosilation of 1-Hexyne with Methyldichlorosilane.**—To a mixture of 14.8 g (0.18 mol) of freshly distilled 1-hexyne (Farchan), 40 μl of chloroplatinic acid solution, and 2 ml of dry benzene was added 17.3 g (0.15 mol) of $MeSiHCl_2$ dropwise during 1.5 hr. An exothermic reaction commenced within 30 min. The reaction mixture was heated at 85° for 7.5 hr after the addition had been completed and then was added to 220 ml of 1.58 M methyllithium in ether (0.34 mol), slowly, with adequate cooling and stirring. The resulting mixture was heated at reflux for 3 hr and then hydrolyzed with 200 ml of water. Fractional distillation of the dried organic phase gave 17.86 g (80%) of the monoaddition product [bp 48–48.5° (13 mm), $n^{25}D$ 1.4248; lit.[24] bp 60° (20 mm), $n^{20}D$ 1.4260].

Anal. Calcd for $C_9H_{20}Si$: C, 69.14; H, 12.89. Found: C, 69.28; H, 12.79.

Glpc analysis of this product using three different columns (Dow Corning DC 200 silicone fluid at 100°, Carbowax 20M at 100°, General Electric Co. XF 1112 at 120°) suggested that only one component was present. The nmr spectrum, however, indicated the presence of a mixture, showing two different Me_3Si resonances at δ 0.12 and 0.16 ppm in area ratio 70:30. Signals at δ 5.59 and 5.34 characteristic of $=CH_2$ protons indicate that the component present in lesser amount is 2-trimethylsilyl-1-hexene, $Me_3Si(n\text{-}C_4H_9)C{=}CH_2$.

Insertion Reactions of Phenyl(bromodichloromethyl)mercury-Derived Dichlorocarbenene. General Procedure.—A three-necked flask of appropriate volume equipped with a reflux condenser topped with an inert gas inlet tube, a magnetic stirring unit, and a thermometer was charged with the mercurial, the substrate, and, in some cases, benzene solvent. The mixture was stirred and heated at reflux in an oil bath maintained at 85–90°, generally for 2.5–3 hr. Initially, the mercurial dissolved as the reaction mixture was heated, and a short time thereafter phenylmercuric bromide began to precipitate. Upon completion of the reaction, the mixture was filtered to remove phenylmercuric bromide (usually formed in above 90% yield). The filtrate was trap-to-trap distilled under vacuum (0.05–0.1 mm) into a receiver cooled to −78°. Glpc analysis of the filtrate usually followed, but, when reactions were carried out on a larger scale, the products were isolated by fractional distillation in vacuum.

Reaction of $PhHgCCl_2Br$ with Cyclohexane.—Thermolysis of 88 g (0.2 mol) of the mercurial was carried out in 275 ml of cyclohexane which was distilled directly into the reaction flask from potassium under argon. Glpc analysis of the trap-to-trap distillate showed the presence of three major components: tetrachloroethylene (26%), cyclohexyl bromide (22%), and (dichloromethyl)cyclohexane (32%) (*n*-butyrophenone internal standard). The first two products were identified by comparison of their glpc retention times and their ir spectra with those of authentic samples. (Dichloromethyl)cyclohexane, $n^{25}D$ 1.4835, showed the following absorptions in its infrared spectrum: 2939 s, 2860 s, 1450 s, 1365 m, 1331 w, 1308 m, 1298 m, 1254 m, 1238 s, 1218 s, 1175 w, 1140 w, 1090 m, 1080 m, 1062 m, 1040 m, 963 s, 927 w, 920 w, 896 m, 885 m, 788 m, 740 s, and 676 s cm^{-1}. Its nmr spectrum showed the following resonances: δ 5.60 (1 H, $-CCl_2H$) d (J = 4.0 Hz), multiplet (11 H) containing two broad resonances at 1.87 and 1.25 ppm.

Anal. Calcd for $C_7H_{12}Cl_2$: C, 50.31; H, 7.24; Cl, 42.44. Found: C, 50.03, 50.31; H, 7.23, 7.47; Cl, 42.29.

The isolated phenylmercuric bromide (77%) was gray in color, which suggests the formation of a minor amount of elemental mercury.

A similar reaction carried out with phenyl(trichloromethyl)-mercury (5 days at reflux) gave tetrachloroethylene, cyclohexyl chloride, and (dichloromethyl)cyclohexane in yields of 10, 4, and 16%, respectively.

Reaction of $PhHgCCl_2Br$ with Methylcyclohexane.—A solution containing 4.45 g (10.2 mmol) of the mercurial, 2.91 g (32.8 mmol) of methylcyclohexane, and 15 ml of dry benzene under nitrogen was used. The filtrate was trap-to-trap distilled under vacuum and then fractionally distilled to give 0.27 g of distillate at 90–95° (5 mm). Glpc (General Electric Co. XF 1150) showed that the latter contained a single component; the yield was 14.6%. An analytical sample was isolated by glpc.

Anal. Calcd for $C_8H_{14}Cl_2$: C, 53.02; H, 7.79; Cl, 39.15. Found: C, 53.20; H, 7.80; Cl, 39.31.

The nmr spectrum confirmed that the product was 1-methyl-1-(dichloromethyl)cyclohexane: the $-CCl_2H$ resonance appeared as a singlet at δ 5.54 ppm, and the ring protons and the CH_3 protons were seen as a broad resonance from 0.7 to 1.6 ppm. The $n^{25}D$ was 1.4876.

Reaction of $PhHgCCl_2Br$ with 2-Methylhexane.—A mixture of 6.60 g (15 mmol) of the mercurial and 4.50 g (45 mmol) of 2-methylhexane (Chemical Samples Co.) was used. Fractional distillation of the filtrate gave 1.47 g of 2-methylhexane and 1.06 g of a higher boiling fraction which glpc showed to be *ca.* 90% pure. A yield determination by glpc (20% UC-W98 at 120°) established that the product, 1,1-dichloro-2,2-dimethylhexane, had been formed in 31% yield. An analytical sample, $n^{25}D$ 1.4528, was isolated by glpc: nmr (in CCl_4) δ 5.62 (1 H, $-CCl_2H$) s, 1.43 [6 H, $-(CH_2)_3-$] m, 1.10 [6 H, $(CH_3)_2C-$] s, 0.96 ppm (3 H, CH_3CH_2-) t (J = 7 Hz).

Anal. Calcd for $C_8H_{16}Cl_2$: C, 52.47; H, 8.81; Cl, 38.72. Found: C, 52.53; H, 8.67; Cl, 39.03.

A reaction carried out with 10 mmol of mercurial and 30 mmol of the hydrocarbon in 15 ml of benzene gave this product in 20% yield.

Reaction of $PhHgCCl_2Br$ with 3-Methylcyclohexene.—A mixture of 10 mmol of the mercurial and 30 mmol of the olefin (no solvent) was used. The filtrate was trap-to-trap distilled in vacuum. Analysis of the distillate by glpc (20% Carbowax 20M) showed the presence of two products in 8.2:1 area ratio. The major product, $n^{25}D$ 1.4938, was identified as 7,7-dichloro-2-methylnorcarane: nmr (in CCl_4) δ 1.21 (3 H, CH_3-) d (J = 6.2 Hz), 0.6–2.2 ppm (9 H) complex multiplet.

Anal. Calcd for $C_8H_{12}Cl_2$: C, 53.65; H, 6.75; Cl, 39.60. Found: C, 53.87; H, 6.74; Cl, 39.57.

The minor product was identified as 3-methyl-3-(dichloromethyl)cyclohexene: nmr (neat) δ 5.3–5.9 (2 H, $-CH{=}CH-$) m, 5.56 (1 H, CCl_2H) s, 0.8–2.2 [6 H, $-(CH_2)_3-$] m, 1.08 ppm (3 H, CH_3) s.

Anal. Found: C, 53.37; H, 6.54.

A yield determination (*n*-undecane internal standard) showed the yields of addition and insertion product to be 76 and 9%, respectively.

Reaction of $PhHgCCl_2Br$ with 1-Trimethylsilyl-3-methyl-1-butene.—The olefin was contaminated with *ca.* 16% 2-trimethylsilyl-3-methyl-1-butene. The reaction was carried out on the same scale using the same procedure. Glpc analysis (20% Carbowax 20M) of the distillate showed the presence of two major products (minor products due to the contaminating isomeric silane were not examined).

The major product (59% yield) was *trans*-1,1-dichloro-2-trimethylsilyl-3-isopropylcyclopropane: $n^{25}D$ 1.4519; nmr (CCl_4) δ 0.9–1.4 (8 H) broad multiplet and a set of four sharp resonances, 0.3 (1 H, Me_3Si–C–*H*) m, 0.12 ppm (9 H, Me_3Si) s.

Anal. Calcd for $C_9H_{18}Cl_2Si$: C, 47.99; H, 8.06. Found: C, 48.01; H, 8.00.

The minor product (27% yield) was *trans*-1-trimethylsilyl-3,3-dimethyl-4,4-dichloro-1-butene: $n^{25}D$ 1.4645; nmr (in CCl_4) δ 6.10 (1 H, =CH *cis* to Me_3Si) d (J = 19.2 Hz), 5.82 (1 H, $=CHSiMe_3$) d (J = 19.2 Hz), 5.56 (1 H, CCl_2H) s, 1.24 [6 H, $(CH_3)_2C$] s, 0.10 ppm (9 H, Me_3Si) s.

Anal. Found: C, 48.21; H, 8.19.

Reaction of $PhHgCCl_2Br$ with 70:30 Mixture of *trans*-1-Trimethylsilyl-1-hexene and 2-Trimethylsilyl-1-hexene.—The reaction was carried out on the same scale using the same procedure.

Glpc analysis (20% Carbowax 20M) showed the presence of two products in 4:1 ratio based on glpc peak areas. The total yield was 75%.

The major product was *trans*-1,1-dichloro-2-trimethylsilyl-3-*n*-butylcyclopropane: nmr (in CCl_4) δ 1.8–0.8 (10 H), two broad resonances, 0.24 (1 H, Me_3SiCH) m, 0.16 ppm (9 H, Me_3Si) s.

Anal. Calcd for $C_{10}H_{20}Cl_2Si$: C, 50.20; H, 8.43; Cl, 29.63 Found: C, 50.53; H, 8.39; Cl, 29.42.

The minor product was 1,1-dichloro-2-trimethylsilyl-2-*n*-butylcyclopropane: nmr (neat) δ 2.0–0.8 (11 H) m, 0.20 ppm (9 H, Me_3Si) s.

Anal. Found: C, 50.04; H, 8.22; Cl, 29.37.

Reaction of $PhHgCCl_2Br$ with Ethylbenzene.—A mixture of 44.0 g (0.1 mol) of the mercurial in 150 ml of freshly distilled ethylbenzene was used. Glpc analysis of the filtrate at 200° detected only one higher boiling component. Trap-to-trap distillation at 0.1 mm (pot temperature to 95°) gave a clear distillate and 2.6 g of black residue. Glpc examination of the former showed the presence of β,β-dichloroisopropylbenzene in 35% yield. Fractional distillation gave 4.81 g of this product: bp 63–65° (0.85 mm); $n^{25}D$ 1.5374 (lit.[13] bp 57° (0.4 mm); $n^{20}D$ 1.5351); nmr (CCl_4) δ 7.29 (5 H, C_6H_5) s, 5.80 (1 H, CCl_2H) d (J = 5.0 Hz), 3.39 (1 H, PhCH) octet, 1.52 ppm (3 H, CH_3) d (J = 7.5 Hz).

Anal. Calcd for $C_9H_{10}Cl_2$: C, 57.16; H, 5.33; Cl, 37.50. Found: C, 57.26; H, 5.23; Cl, 37.28.

A similar experiment in which much greater care was taken to exclude air and in which the ethylbenzene was distilled from potassium benzophenone ketyl gave this product in 37% yield. On the other hand, a reaction of 0.01 mol of the mercurial with 0.05 mol of ethylbenzene in 75 ml of benzene at reflux for 2 hr gave the expected product in only 5% yield, as well as tetrachloroethylene in 4.4% yield.

Reaction of $PhHgCCl_2Br$ with Cumene (Isopropylbenzene).—A suspension of the mercurial (0.2 mol) in 300 ml of cumene under argon was used. Color changes from light yellow to dark orange occurred. Filtration gave phenylmercuric bromide in 96% yield. Trap-to-trap distillation of the filtrate in two fractions, (at 0.5 mm, 35°; and at 0.005 mm, 85°) was followed by glpc analysis of the latter (*n*-butyrophenone internal standard). It was found that β,β-dichloro-*t*-butylbenzene was present in 58% yield. Also present were tetrachloroethylene (4%) and 1,1-dichloro-2-methyl-2-phenylcyclopropane[9] (2%). The distillate was fractionally distilled to give 18.7 g (46%) of β,β-dichloro-*t*-butylbenzene: bp 80–84° (1.5 mm); $n^{26}D$ 1.5400 (lit.[13] bp 68–70° (3 mm), $n^{20}D$ 1.5400); nmr (in CCl_4) δ 7.38 (5 H, C_6H_5) s, 5.98 (1 H, CCl_2H) s, 1.53 ppm [6 H, $C(CH_3)_2$] s.

A similar experiment carried out at 70° for 2 hr gave the insertion product in 54% yield.

Reaction of $PhHgCBr_3$ with Ethylbenzene.—A mixture of 52.95 g (0.1 mol) of the mercurial and 175 ml of ethylbenzene was used. By cooling the dark orange filtrate, the precipitation of 7.8 g of brown solid could be effected. Solvent was removed from the filtrate at 0.1 mm and short-path distillation of the residue at 0.07 mm gave 3.15 g of a viscous liquid containing a small amount of white solid; the maximum pot temperature was 140°. Glpc analysis of the distillate (25% SE-30, short column) showed that β,β-dibromoisopropylbenzene (6.5% yield) was present. A pure sample, $n^{25}D$ 1.5867, was collected by glpc: nmr (in CCl_4) δ 7.34 (5 H, C_6H_5) d, 5.88 (1 H, CBr_2H) d (J = 4.5 Hz), 3.52 (1 H, PhCH) m, 1.60 ppm (3 H, CH_3) d (J = 7.0 Hz).

Anal. Calcd for $C_9H_{10}Br_2$: C, 38.87; H, 3.62; Br, 57.49. Found: C, 39.05; H, 3.71; Br, 57.54.

Registry No.—Phenyl(bromodichloromethyl)mercury, 3294-58-4; *trans*-1-trimethylsilyl-3-methyl-1-butene, 24099-72-7; (dichloromethyl)cyclohexane, 24099-71-6; 1-methyl-1-(dichloromethyl)cyclohexane, 24147-13-5; 1,1-dichloro-2,2-dimethylhexane, 24099-19-2; 7,7-dichloro-2-methylnorcarane, 24099-20-5; 3-methyl-3-(dichloromethyl)cyclohexane, 24099-21-6; *trans*-1,1-dichloro-2-trimethylsilyl-3-isopropylcyclopropane, 24099-73-8; *trans*-1-trimethylsilyl-3,3-dimethyl-4,4-dichloro-1-butene, 24099-74-9; *trans*-1,1-dichloro-2-trimethylsilyl-3-*n*-butylcyclopropane, 24099-75-0; 1,1-dichloro-2-trimethylsilyl-2-*n*-butylcyclopropane, 24099-22-7; β,β-dibromoisopropylbenzene, 24162-41-2.

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Halomethyl Metal Compounds. XXXIII. The Insertion of Phenyl(bromodichloromethyl)mercury-Derived Dichlorocarbene into Carbon–Hydrogen Bonds. Ethers[1]

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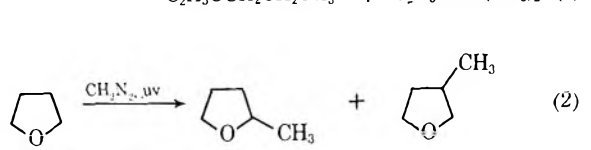
The known insertion of dichlorocarbene into C–H bonds α to the oxygen atom in ethers has received further study using phenyl(bromodichloromethyl)mercury as the dichlorocarbene source. Results are reported for 13 ethers. For C–H bonds α to ether oxygen, the relative reactivity toward CCl_2 was found to be tertiary > secondary, and no insertion was observed at OCH_3 C–H linkages. In over half of the examples cited the insertion product yields were in the preparatively useful range (>40%): diethyl ether, di-*n*-propyl ether, isopropyl methyl ether, benzyl methyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, and 2,5-dimethyltetrahydrofuran.

The insertion of a carbene, CH_2 itself, into a C–H bond of an ether was reported first by Meerwein and his coworkers[3] in 1942 (eq 1 and 2). Subsequent studies by other workers[4–6] have been devoted to obtaining a better understanding of such reactions. An analogous insertion chemistry of dichlorocarbene was developed by Anderson, Lindsay, and Reese,[7]

$$CH_3CH_2OCH_2CH_3 \xrightarrow{CH_2N_2,\ uv} C_2H_5OCH_2CH_2CH_3 + C_2H_5OCH(CH_3)_2 \quad (1)$$



(2)

(1) Part XXXII: D. Seyferth, J. M. Burlitch, K. Yamamoto, S. S. Washburne, and C. J. Attridge, *J. Org. Chem.*, **35**, 1989 (1970).

(2) National Institutes of Health Predoctoral Fellow, 1963–1966.

(3) H. Meerwein, H. Rathjen and H. Werner, *Chem. Ber.*, **75**, 1610 (1942).

(4) W. von E. Doering, L. H. Knox, and M. Jones, Jr., *J. Org. Chem.*, **24**, 136 (1959).

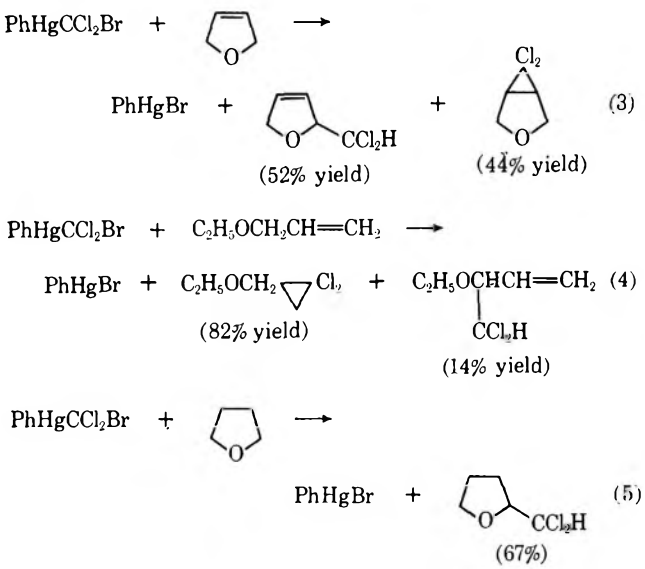
(5) H. M. Frey and M. A. Voisey, *Trans. Faraday Soc.*, **64**, 954 (1968).

(6) M. A. Voisey, *ibid.*, **64**, 3058 (1968).

(7) (a) J. C. Anderson and C. B. Reese, *Chem. Ind.* (London), 575 (1963); (b) J. C. Anderson, D. G. Lindsay, and C. B. Reese, *J. Chem. Soc.*, 4874 (1964).

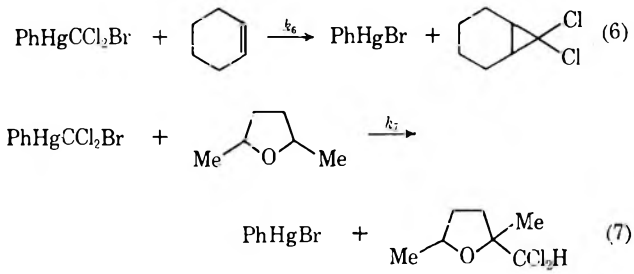
who reported the reactions shown in Table I. Noteworthy in these was (1) the regiospecificity of the CCl_2 insertions which occurred, and (2) the high reactivity of the CH_2 groups of 2,5-dihydrofuran. These reactions did not appear to be very attractive for preparative purposes because of the rather low yields of products which could be realized.

Our previous research had shown that phenyl(bromodichloromethyl)mercury, which releases CCl_2 to a variety of substrates rapidly at 80°, was uniquely useful in transferring dichlorocarbene to reactants which were only poorly reactive toward this intermediate.[1,8] Accordingly, it was of interest to examine the reactions of $PhHgCCl_2Br$ with ethers to see if this interesting but synthetically limited CCl_2 insertion process could not be developed into a more useful one. We have already reported concerning our early work with reactions of this mercury reagent with 2,5-dihydrofuran, ethyl allyl ether, and tetrahydrofuran[8] (eq 3–5). These initial results indicated that $PhHgCCl_2Br$ could be used to good advantage in a study of CCl_2 insertion into C–H bonds of ethers and that the general behavior of this reagent was similar to that of the CCl_2-generating systems used by the English workers.[7]



The results of Reese, *et al.*,[7] had led them to suggest that the factor which is most important in these insertion reactions is the effect of the ether oxygen atom in stabilizing a partial positive charge on the adjacent carbon atom into whose bond to hydrogen such CCl_2 insertion is occurring. However, the very limited number of examples studied (Table I) and the generally low yields obtained in all cases except that of 2,5-dihydrofuran led us to investigate in more detail the insertion of CCl_2 into C–H bonds of ethers using phenyl(bromodichloromethyl)mercury as a CCl_2 source.

First, however, it was of some importance to show that in these reactions we were indeed dealing with insertion of dichlorocarbene into the C–H bond and not with a direct reaction of the organomercurial with the ether. Variable concentration competition experiments, in which mixtures of 2,5-dihydrofuran and cyclohexene were allowed to compete for a deficiency of $PhHgCCl_2Br$, gave some indication that the former was the case. Equations 6 and 7 show the reactions



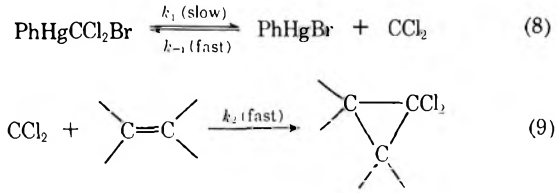
involved. Let it be assumed that the rate of 7,7-dichloronorcarane formation is nth order in mercurial and mth order in cyclohexene and that the rate of 2,5-dimethyl-2-(dichloromethyl)tetrahydrofuran formation is n'th order in mercurial and m'th order in the ether. Then, in the most general case, we would have the rate equations

$$-dO/dt = k_6[PhHgCCl_2Br]^n[O]^m$$
$$-dE/dt = k_7[PhHgCCl_2Br]^{n'}[E]^{m'}$$

where O = the olefin, cyclohexene; E = the ether, 2,5-dimethyltetrahydrofuran. Dividing the second rate equation by the first gives

$$k_{rel} = \frac{k_7}{k_6} = \frac{dE/dt][PhHgCCl_2Br]^n[O]^m}{[dO/dt][PhHgCCl_2Br]^{n'}[E]^{m'}}$$

If the experimental finding is that k_{rel} remains constant as the concentrations of the competing reagents are varied, then n must equal n' and m must equal m'. In other words, the orders of the reaction must be the same for both C=C addition and C–H insertion. If k_{rel} is found to change as the reactant concentrations are varied, then one has good indication that C=C addition and C–H insertion proceed by different mechanisms. In the case of the olefin–$PhHgCCl_2Br$ reaction the mechanism shown in eq 8 and 9 was found to be operative.[9] The competition



of one olefin with another for mercurial-derived CCl_2 involves the second step (k_2). If the ether–mercurial reaction proceeded by a similar course, one would expect to find k_{rel} [k(E)/k(O)] to be unchanged as the relative concentrations of the ether and the olefin were changed. If, on the other hand, the ether–$PhHgCCl_2Br$ reaction proceeded by a mechanism different from that of the olefin–$PhHgCCl_2Br$ reaction, such relative starting concentration changes could bring about changes in the observed k_{rel}.

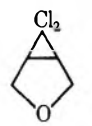
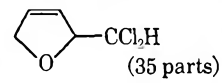
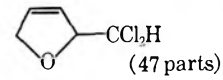
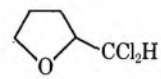
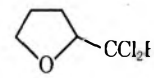
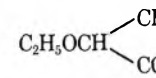
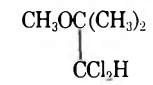
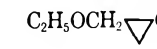
The results of these experiments are shown in Table II. The value of k_{rel} did not change (within experimental error) as the relative concentrations of cyclohexene and 2,5-dimethyltetrahydrofuran were changed from 1:1 to 1:2 to 2:1, respectively. This suggests

(8) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J.-H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

(9) D. Seyferth, J. Y.-P. Mui, and J. M. Burlitch, *ibid.*, **89**, 4953 (1967).

TABLE I

REACTIONS OF DICHLOROCARBENE WITH ETHERS[a]

Ether	CCl_2 source	Product (% yield)
	$CCl_3CO_2Et/NaOMe$	 (65 parts);  (35 parts) (62)
	CCl_3CO_2Na	 (53 parts);  (47 parts) (34)
	$CCl_3CO_2Et/NaOMe$	 (2.5)
	CCl_3CO_2Na	 (3.7)
$(CH_3CH_2)_2O$	$CCl_3CO_2Et/NaOMe$	 (20)
$(CH_3)_2CHOCH_3$	$CCl_3CO_2Et/NaOMe$	 (9)
$C_2H_5OCH_2CH{=}CH_2$	$CCl_3CO_2Et/NaOMe$	 (12.7)

[a] Reference 7.

(but by no means proves) that the $PhHgCCl_2Br$–ether reaction involves CCl_2 as an actual intermediate, and in our further discussions we will assume this to be the most reasonable reaction course.

Our investigation proceeded with a study of the reaction of phenyl(bromodichloromethyl)mercury with 13 ethers (Table III). The yields obtained, as expected, were consistently better than those found with other CCl_2 sources. Thus, for instance, CCl_3CO_2Na inserted CCl_2 into diethyl ether in 20% yield, $PhHgCCl_2Br$ in 54% yield. Sodium trichloroacetate inserted CCl_2 into isopropyl methyl ether in 9% yield; $PhHgCCl_2Br$ did so in 39% yield.

The yields obtained with different ethers in reactions with phenyl(bromodichloromethyl)mercury varied markedly with structure. Using our "standard" mercurial reaction conditions—threefold excess of the ether, reaction in benzene medium at reflux for 4 hr—the yields ranged from 90% in the case of 2,5-dimethyltetrahydrofuran to 3% with neopentyl methyl ether. As the ether yields decreased, the yields of tetrachloroethylene, the product of the reaction of CCl_2 with $PhHgCCl_2Br$,[8] increased.

The following observations are worth special notice since they are relevant to a discussion of the mechanism of this C–H insertion process.

(1) As in the case of hydrocarbons,[1] CCl_2 insertion into C–H bonds is most favorable where the carbon atom involved could stabilize a partial positive charge. This is shown by the series benzyl methyl ether (71%), isopropyl methyl ether (40%), *n*-propyl methyl ether (10%) (Table III). No insertion into a OCH_3 group was observed in any case. With 2-methyltetrahydrofuran, insertion of CCl_2 into the tertiary C–H bond is favored over insertion into the secondary C–H bond by a factor of 8. Electronegative substituents appear to deactivate C–H bonds in this reaction. Thus in the case of $ClCH_2CH_2OCH_2CH_3$, dichlorocarbene insertion occurs only into the ethyl group.

TABLE II

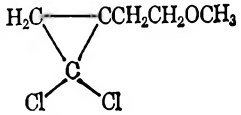
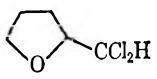
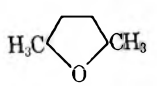
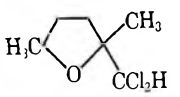
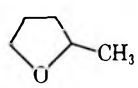
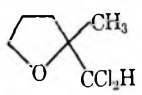
COMPETITION EXPERIMENTS. REACTION OF MIXTURES OF CYCLOHEXENE AND 2,5-DIMETHYLTETRAHYDROFURAN WITH A DEFICIENCY OF PHENYLMERCURIC BROMIDE IN BENZENE at 80 ± 2°

Initial reactant ratio, moles of $PhHgCCl_2Br$/moles of olefin (O)/moles of ether (E)	$k_{rel} = k(E)/k(O)$
1/5/5	0.169, 0.174
1/5/10	0.173, 0.165
1/10/5	0.158, 0.162

(2) Dichlorocarbene insertion into C–H bonds α to the ether function was highly favored. Isobutyl methyl ether with a tertiary C–H bond β to the oxygen and a secondary C–H bond α to the oxygen gave $Me_2CHCH(CCl_2H)OMe$ as the major product on reaction with $PhHgCCl_2Br$. A minor product, tentatively identified as $Me_2(CCl_2H)CCH_2OMe$, also was produced. Tetrahydrofuran, with secondary C–H bonds both α and β to the oxygen, underwent reaction only at the former. This is in marked contrast to

TABLE III

REACTIONS OF PHENYL(BROMODICHLOROMETHYL)MERCURY WITH ETHER

Ether	Insertion product	Yield, %
$CH_3CH_2OCH_2CH_3$	$CH_3CHOCH_2CH_3$ CCl_2H	58, 51
$CH_3CH_2CH_2OCH_2CH_2CH_3$	$CH_3CH_2CHOCH_2CH_2CH_3$ CCl_2H	42, 40
$CH_3CH_2CH_2OCH_3$	$CH_3CH_2CHOCH_3$ CCl_2H	10
$(CH_3)_2CHOCH_3$	$(CH_3)_2COCH_3$ CCl_2H	41, 38
$(CH_3)_3CCH_2OCH_3$	$(CH_3)_3CCHOCH_3$ CCl_2H	2, 5
$(CH_3)_2CHCH_2OCH_3$	$(CH_3)_2CHCHOCH_3$ CCl_2H	7
	$(CH_3)_2CCH_2OCH_3$[a] CCl_2H	2
$ClCH_2CH_2OCH_2CH_3$	$ClCH_2CH_2OCHCH_3$ CCl_2H	16, 14
$C_6H_5CH_2OCH_3$	$C_6H_5CHOCH_3$ CCl_2H	69, 73
$CH_2=CHCH_2CH_2OCH_3$		83
		89
		87, 94
		78, 80
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	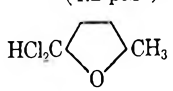	
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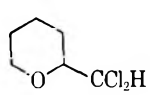
		18, 20

[a] Identification tentative.

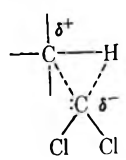
CH_2 (*via* CH_2N_2 photolysis) insertion into C–H bonds of ethers. The insertion of CH_2 into tetrahydrofuran was not restricted to the α C–H bonds; insertion into β C–H bonds occurred as well, the α/β C–H insertion ratio being 1.26.[4] In the case of diethyl ether, the ratio of $EtOCH_2CH_2CH_3$ to $EtOCH(CH_3)_2$ formed, 55.5:44.5, was close to the statistical value.[4]

(3) An isolated terminal C=C bond is much more reactive than a C–H bond adjacent to an ether function. With $CH_2=CHCH_2CH_2OCH_3$ *only* the expected *gem*-dichlorocyclopropane was obtained. However, when the double bond is so situated that the C–H bond adjacent to the oxygen atom is also allylic (*e.g.*, allyl ethyl ether), then this C–H linkage diverts some CCl_2 from the C=C bond (eq 4).[8] Such a C–H bond becomes even more reactive when it is contained in a five-membered ring (eq 3).

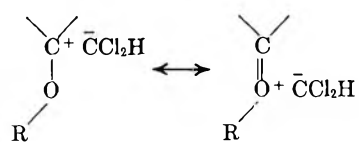
(4) Steric hindrance does appear to play a role. A *t*-butyl group strongly hinders attack at the α C–H bonds of Me_3CCH_2OMe, just as the *t*-amyl group strongly deactivated a vinyl group (in $Me_2EtCCH=CH_2$) toward CCl_2 addition.[10]

(5) Five-membered cyclic ethers enjoy an especially high reactivity, as the comparison between tetrahydrofuran and tetrahydropyran shows. When the C–H bond in question is a tertiary one, adjacent to an ether function and contained in a five-membered ring, the activating influences combine to give maximum reactivity. However, even this most favorable ether is less reactive toward CCl_2 than a "normal" C=C bond. In the case of 2,5-dimethyltetrahydrofuran, the relative reactivity *per C–H bond vs.* the C=C bond of cyclohexene is *ca.* 0.085. By comparison, the relative reactivity of 1-heptene *vs.* cyclohexene is *ca.* 0.24.

In our discussion of CCl_2 insertion into C–H bonds of alkanes and alkylbenzenes,[1] we favored a process in which there is some development of charge in the transition state, as shown in I. Alkyl and aryl substituents which could by their inductive and resonance effects, respectively, stabilize the partial positive charge on carbon facilitated such insertion. Such a transition state would also serve to explain the activation of C–H bonds toward CCl_2 insertion by an adjacent ether function. In the extreme case, such stabilization would be as shown in II, but complete ionization need not (and most likely does not) occur for such stabilization to be important.

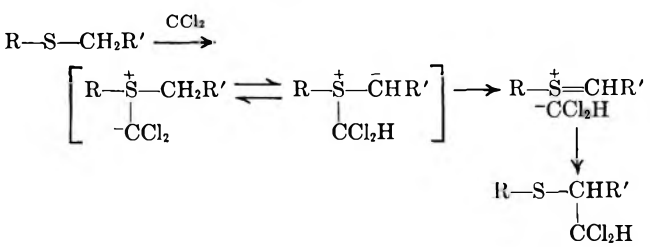


I



II

Similar insertion of CCl_2 into C–H bonds α to a thioether function has been described by Parham and his coworkers, and these reactions were shown to occur by the path indicated below.[11] We see no need



(10) D. Seyferth and H. Dertouzos, *J. Organometal. Chem.*, **11**, 263 (1968).

(11) (a) W. E. Parham and R. Koncos, *J. Amer. Chem. Soc.*, **83**, 4034 (1961); (b) W. E. Parham, L. Christensen, S. H. Groen, and R. M. Dodson, *J. Org. Chem.*, **29**, 2211 (1964); (c) W. E. Parham and S. H. Groen, *ibid.*, **29**, 2214 (1964); (d) *ibid.*, **30**, 3181 (1965); (e) *ibid.*, **30**, 728 (1965).

to postulate similar initial attack by CCl_2 at the oxygen atom of the ether molecule undergoing insertion. Further examples of reactions of $PhHgCCl_2Br$ with cyclic, allylic methyl ethers will be reported elsewhere.[12]

Experimental Section

General Comments.—All reactions were carried out under an atmosphere of prepurified nitrogen or argon. Infrared spectra were recorded using a Perkin-Elmer 237B or 337 grating infrared spectrophotometer. Nmr spectra were obtained using a Varian Associates A-60 nmr spectrometer. Chemical shifts are given in δ units, parts per million downfield from internal TMS. Gas–liquid partition chromatography (glpc) was accomplished using either an MIT isothermal unit or commercial F & M gas chromatographs (Models No. 700, 776 and 5750). Unless otherwise noted, the columns were packed with 20–25% silicone oil (Dow Corning 200) or silicone rubber gum (General Electric Co. SE-30) on Chromosorb P or W. Phenyl(bromodichloromethyl)mercury was prepared by our published procedures.[13,14] The ethers used either were commercial products whose purity was checked before use or were prepared in a straightforward manner by the Williamson synthesis. The physical properties (boiling point and refractive index and the ir and/or nmr spectrum in some cases) were in good agreement with those given in the literature.

The Reaction of Phenyl(bromodichloromethyl)mercury with Ethers. General Procedure.—Into a 50- or 100-ml three-necked flask was charged under nitrogen or argon 0.03 mol of the ether, 4.4 g (0.01 mol) of the mercurial, and 15 ml of dry benzene. The reaction flask was equipped with a magnetic stirring assembly and a reflux condenser topped with a nitrogen inlet tube. The reaction mixture was stirred and heated at reflux (oil-bath temperature 88–95°) for 3 hr. During this time flaky, crystalline phenylmercuric bromide precipitated. Upon completion of the heating period the reaction mixture was filtered to remove PhHgBr (the yields were *ca.* 90%—lower than in the case of reactions with olefins, presumably because of the greater solubility of phenylmercuric bromide in the medium containing unconverted ether). A high-vacuum (0.05–0.2 mm) trap-to-trap distillation of the filtrate followed, and subsequently the distillate was examined by glpc. Products were isolated by preparative glpc and characterized. Yields were determined by glpc using the internal standard method. Details concerning the products obtained in the individual experiments follow below.

Diethyl ether gave 1,1-dichloro-2-ethoxypropane

$$CH_3CH_2OCHCH_3$$
$$\quad\quad|$$
$$\quad CCl_2H$$

in 58% yield (51% in a duplicate experiment), together with tetrachloroethylene in 8% yield. The insertion product had $n^{25}D$ 1.4371; nmr (microcell, neat) δ 5.8 (1 H, CCl_2H, d, J = 4 Hz), 3.6 (3 H, m), 1.2 (6 H, m).

Anal. Calcd for $C_5H_{10}OCl_2$: C, 38.24; H, 6.42; Cl, 45.15. Found: C, 38.58; H, 6.59; Cl, 45.35.

Di-*n*-propyl ether gave 1,1-dichloro-2-*n*-propoxybutane

$$n\text{-}C_3H_7OCHCH_2CH_3$$
$$\quad\quad\quad|$$
$$\quad\quad CCl_2H$$

in 42 (40) % yield, as well as tetrachloroethylene (15, 13%). The product had $n^{25}D$ 1.4398. The CCl_2H resonance was observed as a doublet (J = 4 Hz) at 5.65 ppm in the nmr spectrum (CCl_4).

Anal. Calcd for $C_7H_{14}OCl_2$: C, 45.42; H, 7.62; Cl, 38.31. Found: C, 45.74; H, 7.60; Cl, 38.27.

***n*-Propyl methyl ether** gave 1,1-dichloro-2-methoxybutane

$$C_2H_5CHOCH_3$$
$$\quad\quad|$$
$$\quad CCl_2H$$

$n^{25}D$ 1.4437, in 10 (5) % yield, as well as tetrachloroethylene (14, 16%): nmr (in CCl_4) δ 5.66 (1 H, CCl_2H, d J = 9 Hz), 3.89–3.07 (1 H, -CHO-, m), 3.42 (3 H, OCH_3, s), 1.67 (2 H, $-CH_2-$, m), 0.99 (3 H, CH_3CH_2, t, J = 13 Hz).

Anal. Calcd for $C_5H_{10}OCl_2$: C, 38.24; H, 6.42; Cl, 45.15. Found: C, 38.18; H, 6.24; Cl, 44.96.

Isopropyl methyl ether gave 2,2-dichloro-1,1-dimethylethyl methyl ether

$$(CH_3)_2C—OCH_3$$
$$\quad\quad|$$
$$\quad CCl_2H$$

$n^{25}D$ 1.4480, in 41 (38)% yield, together with tetrachloroethylene (15, 19%): nmr (CCl_4) δ 5.5 (1 H, CCl_2H, s), 3.13 (3 H, OCH_3, s), 1.22 [6 H, $(CH_3)_2C$, s].

Anal. Calcd for $C_5H_{10}OCl_2$: C, 38.24; H, 6.42; Cl, 45.15. Found: C, 38.15; H, 6.50; Cl, 44.93.

Isobutyl methyl ether gave tetrachloroethylene (24%) and a 1.5/6.25/1.0 mixture of products that could be separated into the individual components using a 20% Carbowax column at 105°. The total product yield was estimated by glpc to be 12%. The major component was 1,1-dichloro-2-methoxy-3-methylbutane

$$(CH_3)_2CHCHOCH_3$$
$$\quad\quad\quad|$$
$$\quad\quad CCl_2H$$

$n^{25}D$ 1.4436; nmr (neat) δ 5.55 (1 H, CCl_2H, d, J = 6 Hz), 3.55 (3 H, OCH_3, s), 3.15 (1 H, $CHOCH_3$ doublet of doublets, J = 4 and 6 Hz), 2.15 (1 H, Me_2CH, m), 1.0 and 0.9 [6 H, $(CH_3)_2C$, two superimposed doublets, J = 6 Hz for each]; mass spectrum 170, parent ion (M:M + 2 = 3:2), 87, molecular ion (M − CCl_2H^+), 127 = 2% $CH_3OCHCHCl_2^+$.

Anal. Calcd for $C_6H_{12}OCl_2$: C, 42.12; H, 7.07. Found: C, 42.47; H, 7.17.

The minor products were not identified. The one with lower glpc retention time showed a band at 2820 cm^{-1} in its ir spectrum (characteristic of an OCH_3 group[15]) and also bands attributable to C–Cl linkages [765 (vs), 710 (m)] and thus may be the other isomer

$$(CH_3)_2C—CH_2OCH_3$$
$$\quad\quad|$$
$$\quad CCl_2H$$

Neopentyl methyl ether gave 1,1-dichloro-2-methoxy-3,3-dimethylbutane

$$(CH_3)_3CCHOCH_3$$
$$\quad\quad\quad|$$
$$\quad\quad CCl_2H$$

$n^{25}D$ 1.4538, in 5 (2) % yield and tetrachloroethylene (33, 30%): nmr (CCl_4) δ 5.89 (1 H, CCl_2H, d, J = 5 Hz), 3.67 (3 H, OCH_3, s), 3.5 (1 H, CH-OCH_3 d, J = 5 Hz), 1.01 [9 H, $(CH_3)_3C$, s]; mass spectrum 184, parent ion (184:186:188 = 9:6:1, thus 2 chlorines), 92, molecular ion (184 − Cl − Me_3C^+), 101 = 83% (184 − CCl_2H^+).

Anal. Calcd for $C_7H_{14}OCl_2$: C, 45.42; H, 7.62; Cl, 38.31. Found: C, 45.80; H, 7.56; Cl, 38.40.

2-Chloroethyl ethyl ether gave 1,1-dichloro-2-β-chloroethoxypropane

$$ClCH_2CH_2OCHCH_3$$
$$\quad\quad\quad|$$
$$\quad\quad CCl_2H$$

$n^{25}D$ 1.4750, in 16 (14)% yield, as well as tetrachloroethylene (16, 15%): nmr (CCl_4) δ 5.73 (1 H, CCl_2H, d, J = 9 Hz), 3.45–4.0 (5 H, CH_2CH_2OCH, m), 1.4 (3 H, CH_3, d, J = 12.5 Hz); mass spectrum 190, parent ion (190:192:194:196 = 27:

(12) D. Seyferth and V. A. Mai, in preparation; V. A. Mai, Ph.D. Thesis, MIT, 1969.

(13) D. Seyferth and J. M. Burlitch, *J. Organometal. Chem.*, **4**, 127 (1965).

(14) D. Seyferth and R. L. Lambert, Jr., *ibid.*, **16**, 21 (1969).

(15) K. Nakanishi, "Practical Infrared Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 36.

27:9:1, thus 3 chlorine atoms), 63, molecular ion ($ClCH_2CH_2^+$), 107 = 92% ($M - CCl_2H^+$).

Anal. Calcd for $C_5H_9OCl_3$: C, 31.36; H, 4.74. Found: C, 31.39; H, 4.50.

3-Butenyl methyl ether gave 1,1-dichloro-2-β-methoxyethylcyclopropane, $n^{25}D$ 1.4539, as the sole product in 83% yield: nmr δ 3.24 (3 H, OCH_3, s), 3.21 (2 H, CH_2O, t, J = 5.5 Hz), 1.63 (3 H, $CH-CH_2$, m), 1.02 [2 H, CH_2 (ring), m]. No absorptions due to a C=C bond were apparent in the ir spectrum.

Anal. Calcd for $C_6H_{10}OCl_2$: C, 42.63; H, 5.96; Cl, 41.94. Found: C, 42.62; H, 5.96; Cl, 42.18.

Benzyl methyl ether gave 1-methoxy-2,2-dichloroethylbenzene, $n^{25}D$ 1.5305, in 69 (73) % yield, together with a small amount of tetrachloroethylene (3, 6% yield): nmr (CCl_4) δ 7.32 (5 H, C_6H_5, s), 5.75 (1 H, CCl_2H, d, J = 11 Hz), 4.37 (1 H, CHOMe, d, J = 11 Hz), 3.28 (3 H, OCH_3, s); mass spectrum 204, parent ion (204:206:208 = 9:6:1, thus 2 Cl atoms), 77 = 31% $C_6H_5^+$, 91 = 17% $C_6H_5CH_2^+$.

Anal. Calcd for $C_9H_{10}OCl_2$: C, 52.71; H, 4.92. Found: C, 52.88; H, 4.98.

2,5-Dimethyltetrahydrofuran gave 2-dichloromethyl-2,5-dimethyltetrahydrofuran,[16] $n^{25}D$ 1.4645, in 87 (79)% yield: nmr (CCl_4)[16] δ 5.54 (1 H, CCl_2H, s), 4.09 (1 H, CH_3CHO, m), 1.45–2.35 (4 H, CH_2CH_2, m), 1.38 [3 H, $CH_3(CCl_2H)C$, s], 1.21 (3 H, CH_3CH, d, J = 7.5 Hz).

Anal. Calcd for $C_7H_{12}OCl_2$: C, 45.92; H, 6.61; Cl, 38.73. Found: C, 45.80; H, 7.01; Cl, 38.70.

2-Methyltetrahydrofuran gave 2-dichloromethyl-2-methyltetrahydrofuran, $n^{25}D$ 1.4723, and 2-dichloromethyl-5-methyltetrahydrofuran in 4.2:1 ratio in 78 (80)% combined yield: nmr of the major product (CCl_4) δ 5.53 (1 H, CCl_2H, s), 4.28–4.37 (2 H, CH_2O, m), 1.6–2.5 (4 H, CH_2CH_2, m), 1.3 (3 H, CH_3, s). In the nmr spectrum of the minor product a doublet (J = 8 Hz) at 5.68 ppm spoke for the structure indicated.

Anal. Calcd for $C_6H_{10}OCl_2$: C, 42.63; H, 5.96; Cl, 41.94. Found: C, 42.80; H, 6.20; Cl, 41.80.

Tetrahydropyran gave 2-dichloromethyltetrahydropyran in 18 (20) % yield, as well as tetrachloroethylene (12, 12%). The product was rather unstable, turning yellow within a few minutes after isolation by glpc and black within a day in a sealed capillary tube: nmr (CCl_4) δ 5.47 (1 H, CCl_2H, d, J = 5 Hz), 3.0–4.1 (3 H, CH_2OCH, m), 1.0 (6 H, m); mass spectrum 188, parent ion (188:200:202 = 9:6:1, thus 2 Cl atoms), 85, molecular ion ($M - CCl_2H^+$).

Anal. Calcd for $C_6H_{10}OCl_2$: C, 42.63; H, 5.96. Found: C, 42.20; H, 6.03.

Competition Study. Reaction of Mixtures of Cyclohexene and 2,5-Dimethyltetrahydrofuran with a Deficiency of Phenyl(bromodichloromethyl)mercury.—In a typical experiment, a dry, 50-ml flask, equipped with a reflux condenser, a 60-ml pressure-equalizing dropping funnel, a magnetic stirring assembly, and an internal thermometer, was charged with 4.41 g (0.010 mol) of the mercurial, evacuated for 2 hr, and refilled with dry, prepurified nitrogen. Then 15 ml of benzene (distilled from calcium hydride), 4.14 g (0.0504 mol) of cyclohexene (distilled from CaH_2), and 5.19 g (0.0517 mol) of 2,5-dimethyltetrahydrofuran (distilled from CaH_2) were added. The reaction mixture was immersed in an oil bath preheated to 80 ± 2° and stirred at this temperature for 3 hr. During this time the solution turned pale brown and phenylmercuric bromide precipitated. Filtration afforded 3.26 g (92%) of phenylmercuric bromide, mp 284–286°. The filtrate was trap-to-trap distilled at 0.02 mm (pot temperature to 80°). Glpc analysis of the distillate with *o*-dichlorobenzene as internal standard followed. It was established that 7,7-dichloronorcarane and 2-dichloromethyl-2,5-dimethyltetrahydrofuran were present in yields of 75.8% and 13.2%, respectively, giving a k_{rel} of 0.169 (calculation by the method of Doering and Henderson[17]). A duplicate experiment gave these products in yields of 76.5% and 12.8%; k_{rel} = 0.174.

Registry No.—Phenyl(bromodichloromethyl)mercury, 3294-58-4; 1,1-dichloro-2-ethoxypropane, 923-03-5; 1,1-dichloro-2-*n*-propoxybutane, 24165-84-2; 1,1-dichloro-2-methoxybutane, 24165-85-3; 2,2-dichloro-1,1-dimethylethyl methyl ether, 918-43-4; 1,1-dichloro-2-methoxy-3-methylbutane, 24165-87-5; 1,1-dichloro-2-methoxy-3,3-dimethylbutane, 24165-88-6; 1,1-dichloro-2-β-chloroethoxypropane, 24165-89-7; 1,1-dichloro-2-β-methoxyethylcyclopropane, 24165-90-0; 1-methoxy-2,2-dichloroethylbenzene, 24165-91-1; 2-dichloromethyl-2,5-dimethyltetrahydrofuran, 24165-92-2; 2-dichloromethyl-2-methyltetrahydrofuran, 24215-80-3; 2-dichloromethyl-5-methyltetrahydrofuran, 24165-93-3; 2-dichloromethyltetrahydropyran, 24165-94-4.

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(16) First prepared by S. S. Washburne, Ph.D. Thesis, MIT, 1968.

(17) W. von E. Doering and W. A. Henderson, *J. Amer. Chem. Soc.*, **80**, 5274 (1958).

Alumina: Catalyst and Support. XXXIX.[1] Benzyl Migration during the Dehydration of 2,2-Dimethyl-3-phenyl-1-propanol over Alumina Catalysts[2]

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The dehydration of 2,2-dimethyl-3-phenyl-1-propanol at 275–400° over alumina prepared from aluminum isopropoxide was investigated by the micropulse technique. The migratory aptitude ratio of methyl/benzyl was found to be 2.7 and to be constant in the temperature range studied. The suggested mechanism consists of the concerted removal of the hydroxyl group of the alcohol by the intrinsic acidic sites of the catalyst and the abstraction of either an α or a γ proton by the basic sites. γ-Methyl proton abstraction was responsible for 31.5% of the products, whereas 27.2% was from γ-benzyl proton abstraction and 41.3% from α-proton abstraction. Comparisons made with studies of solvolytic reactions of this system support the concept of alumina acting as a "pseudo solvent."

Investigations of the alumina-catalyzed dehydration of alcohols have recently been reviewed by Pines and Manassen[3] and by Knözinger.[4] It was concluded in both reviews that the dehydration of alcohols over alumina occurs by the concerted removal of the hydroxyl group of the alcohol by an acidic site of the catalyst and the abstraction of a proton of the alcohol by a basic site. The similarity between solvolytic elimination reactions and alumina-catalyzed reactions has led to the concept of alumina acting as a "pseudo solvent" which surrounds the alcohol molecule.[3]

Skeletal rearrangement has been observed during some dehydration reactions. Phenyl migrated about eight times as readily as methyl during the dehydration of 2-phenyl-1-propanol-1-^{14}C.[5]

In the reactions of ketones with diazomethane which involve migration to an electron-deficient carbon atom,[6] in the formolysis and acetolysis of 2,2-dimethyl-3-phenyl-1-propyl *p*-toluenesulfonate in which ionization and rearrangement are likely concerted,[7,8] and in the deamination of 2,2-dimethyl-3-phenyl-1-propylamine,[7] methyl was found to have a higher migratory aptitude than benzyl.

The present study of the dehydration of 2,2-dimethyl-3-phenyl-1-propanol over alumina offered a comparison of the migratory aptitudes of benzyl and methyl groups as well as a comparison with elimination reactions in solution on this system.

Procedure.—The dehydration was studied by the micro pulse technique which was first used by Emmett and coworkers[9] and was later modified by Steingaszner and Pines.[10] The detailed experimental procedure was described previously.[11] The material consisting of 8 μl of a mixture of 43.1% alcohol, 4.5% *sec*-butylbenzene, the internal standard used to determine the conversion of alcohol to olefin, and 52.4% cyclohexane, the solvent, was injected by means of a syringe into the microreactor. Helium flowing at a rate of 81 ml/min carried the sample over the catalyst and directly to a gas chromatograph.

Alumina prepared from aluminum isopropoxide according to the procedure of Schappell and Pines[11] and of 20–40 mesh size was used in amounts of 5 to 25 mg. The temperature of the catalyst was varied from 275 to 400°.

Results and Discussion

The dehydration of 2,2-dimethyl-3-phenyl-1-propanol over alumina yielded 2-benzyl-1-butene (**1**), *cis*-(**2**) and *trans*-2-methyl-1-phenyl-1-butene (**3**), 2-benzyl-2-butene (**4**), 3-methyl-1-phenyl-2-butene (**5**), and 2-methyl-4-phenyl-1-butene (**6**). Figures 1 and 2 show the product distribution from the dehydration at 300 and 380°, respectively, and at various conversions effected by changes in the amount of catalyst used. Similar results were found at 275, 340, and 400°.

In Figures 1 and 2, extrapolation to zero conversion gives the initial product distribution. The decrease in **1** and **6** and the increase in **3**, **4**, and **5** as the conversion was increased indicate that some isomerization occurred. At higher temperatures, more isomerization was found.

In an effort to determine further the primary products of the reaction, the catalyst was treated with pyridine. Beranek, *et al.*, showed that, when alumina was treated with pyridine, the isomerizing ability of the catalyst was almost absent, whereas the dehydrating ability was only slightly decreased.[12] Table I shows the effect of this treatment upon the isomerization of 2-benzyl-2-butene (**4**).

2-Phenyl-1-propanol was injected with compound **4** to study isomerization under conditions similar to those during the dehydration reaction. Less isomerization occurred when alcohol was present than when pure olefin was injected. Pyridine treatment of the catalyst reduced the amount of isomerization but a retreatment had no additional effect. An increase in temperature caused more isomerization to occur.

Results of dehydrations over the pyridine-treated alumina are included in Figures 1 and 2. Figure 2 shows that product distribution changes at high con-

(1) (a) For paper XXXVIII, see H. Pines and M. Abramovici, *J. Org. Chem.*, **34**, 70 (1969). (b) Paper XV of the series of Dehydration of Alcohols. For XIV, see E. J. Blanc and H. Pines, *ibid.*, **33**, 2035 (1968).

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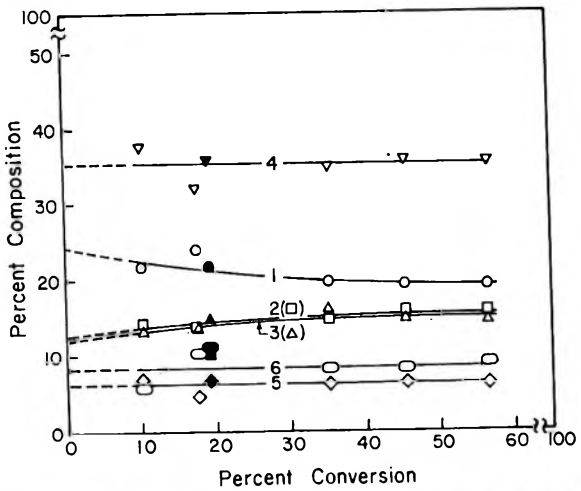


Figure 1.—Composition of olefins from the dehydration of 2,2-dimethyl-3-phenyl-1-propanol at 300° over Al_2O_3 (open symbols) and pyridine-treated Al_2O_3 (filled symbols).

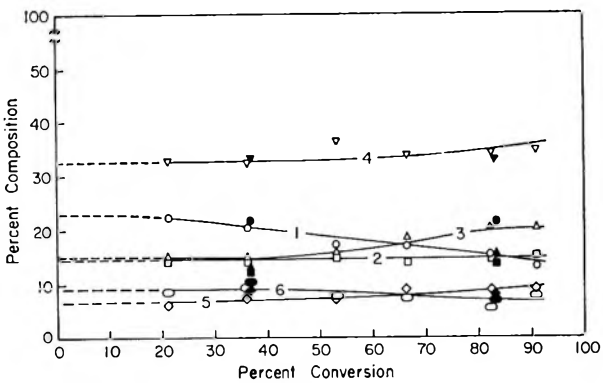


Figure 2.—Composition of olefins from the dehydration of 2,2-dimethyl-3-phenyl-1-propanol at 380° over alumina (open symbols) and pyridine-treated alumina (filled symbols).

TABLE I

EFFECT OF PYRIDINE UPON THE ISOMERIZATION OF 2-BENZYL-2-BUTENE OVER ALUMINA

Expt	Catalyst, mg	Temp, °C	Sample, μl	% unisomerized 2-benzyl-2-butene (4)
1	10	300	4, 1	83.1
2	10[a]	300	4, 1	96.5
3	10	300	4, 1, and PhCCOH, 4 (C)	94.0
4	10[a]	300	4, 1.2, and PhCCOH, 5 (C)	98.1
5	15	325	4, 3	69.3

[a] 15-μl portions of pyridine and three 10-μl portions of a 50:50 cyclohexanol–pyridine mixture were injected at a helium flow of 20 ml/min.

versions are the result of isomerization, since the distribution over pyridine-treated catalyst at high conversions corresponds to that at lower conversions over untreated catalyst.

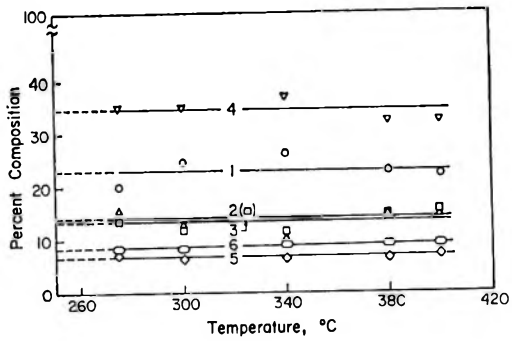


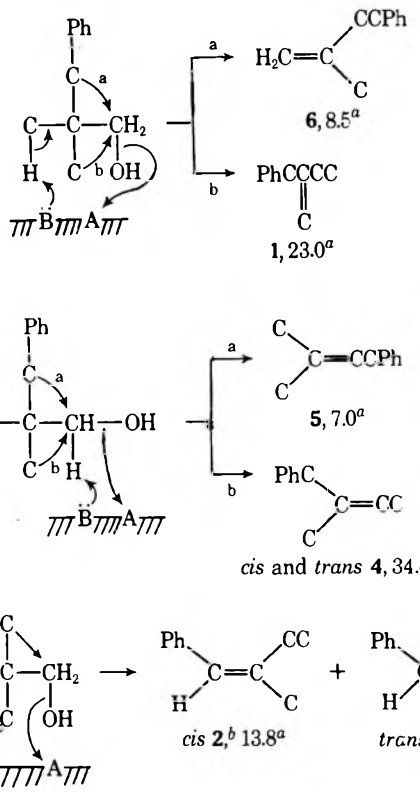
Figure 3.—The effect of temperature upon the product distribution at zero conversion from the dehydration of 2,2-dimethyl-3-phenyl-1-propanol.

Product **1** isomerizes at high conversions and temperatures to **2** and especially to **3** since in these, the double bond is conjugated with the phenyl group. More of olefin **3** than **2** would be expected to be formed since the *trans* isomer is presumably more stable than the *cis*. The small amount of isomerization of product **6** to **5** found is due to the fact that **5**, a trisubstituted olefin, is more stable than **6**, a disubstituted one. Similarly, the slight increase in **4** can be explained by isomerization of **1** to the more stable **4**; the latter is presumably a mixture of *cis* and *trans* isomer, which could not be resolved by vpc.

Extrapolated values for the product distribution at zero conversion are plotted *vs.* temperature in Figure 3 which shows that the initial product distribution, in contrast to the actual distribution, was fairly constant within the temperature range studied.

The formation of the products can be pictured as shown in Chart I.

CHART I



[a] Initial product distribution. [b] The absolute assignment was not made.

TABLE II
GAS CHROMATOGRAPHIC COLUMNS

Columns	% substrate	Solid support[a] (mesh)	Length, m	Outer diameter,[b] in.
A	15% Reoplex[c] 400	Gas Pack WAB (60–80)	3.6	0.375
B	15% Ucon[d] 75H 90,000	Gas Pack WAB (60–80)	4	0.25
C	8% Apiezon L[e]–8% Bentone 34[f]	Gas Pack W (80–100)	4	0.25
D	10% GE XF-1150[g]	Gas Pack W (80–100)	5	0.25

[a] Gas Pack W is a diatomaceous earth. [b] Columns were made of copper. [c] Reoplex is polypropylene glycol adipate. [d] Ucon is a polypropylene glycol. [e] Apiezon L is a high molecular weight hydrocarbon grease. [f] Bentone 34 is dimethyldioctadecylammonium bentonite. [g] GE XF-1150 is a silicone fluid.

The relative migratory aptitude of methyl/benzyl in 2,2-dimethyl-3-phenyl-1-propanol, based upon the extrapolated initial product distributions from Figure 3 and corrected for the statistical factor of two methyl groups, is 2.7.

Warrick and Saunders[7,8] reported finding benzyl migration in the acetolysis of 2,2-dimethyl-3-phenyl-1-propyl *p*-toluenesulfonate and in the deamination of the amine. Although products **1–6** were found in their study, the compounds formed by the removal of a methyl γ hydrogen, **1** and **6**, amounted to 2.36 and 1.64%, respectively, compared with 23.0 and 8.5%, respectively, in the present investigation.

The migratory aptitude of methyl/benzyl is 1.85 in the acetolysis reaction and 2.55 in the formolysis reaction,[8] which is in accordance with the present study.

The fact that the alumina-catalyzed dehydration and these solvolysis reactions yield the same elimination products and similar migratory aptitude ratios supports the concept of alumina acting as a "pseudo solvent".

Experimental Section

Apparatus.—The apparatus used has been described by Steingaszner and Pines[10] and consisted of a microreactor in a furnace, a temperature control panel, and an F & M Model 300 programmed temperature gas chromatograph.

The 150-mm microreactor was constructed of 0.25-in.-o.d. stainless steel tubing. It had stainless steel swagelok fittings on each end and a thermocouple tube welded to the side. A 0.125-in.-o.d. transfer line connected the reactor outlet to the chromatograph inlet.

Analytical Procedures. Gas Chromatographic Columns.—Listed in Table II are the columns used for the dehydration product analyses and preparative gas chromatographic separations.

Identification of the Olefinic Reaction Products.—The reaction products were identified by comparison of their relative retention times with those of known samples. An electronic integrator, Model CRS-11HSB, Infotronics Corp., Houston, Texas, was used to measure chromatographic peak areas.

Since at least two products overlapped on all columns tried, it was necessary to use two separate columns and therefore, to do each run twice under the same experimental conditions. With column C, the 2-methyl-4-phenyl-1-butene (**6**) and 2-benzyl-2-butene (**4**) peaks overlapped. Using column D, the percentage of **4** formed was found. By subtracting this percentage from the combined percentage of **4** and **6** as found on column C, the percentage of **6** formed was determined. The percentages of all other olefinic products were determined by using column C.

2,2-Dimethyl-3-phenylpropanol.—This alcohol was prepared in an overall yield of 23% from benzyl chloride and methyl isobutyrate.[7]

2-Methyl-4-phenyl-1-butene (6) and 3-methyl-1-phenyl-2-butene (5) were prepared by Warrick and Saunders,[7] who kindly supplied us with samples of each.

***cis*- (2) and *trans*-2-Methyl-1-phenyl-1-butene (3), 2-Benzyl-2-butene (4), and 2-Benzyl-1-butene (1).**—A mixture of the four olefins prepared by Warrick and Saunders[7] was separated into pure olefins by means of preparative gas chromatography on column A. The compounds were identified by comparison of their relative retention times on column B with the reported times on a similar column.[7] Their relative retention times at 130° were as follows: compound **1**, 1.00; **4**, 1.19; **2**, 1.28; **3**, 1.44.

The relative retention times of the products from the dehydration of 2.2-dimethyl-3-phenyl-1-propanol were analyzed on columns C at 130° and D at 110° with a helium flow rate of 81 ml/min, and using *sec*-butylbenzene as an internal standard with a retention time of 1.00. On column C the retention times were as follows: compound **1**, 1.86; **4**, 2.16; **6**, 2.16; **5**, 2.59; **2**, 2.70; **3**, 2.96. On column D the retention times were as follows: **1**, 2.00; **4**, 2.30; **2**, 2.56; **6**, 2.56; **5**, 2.72; **3**, 2.94.

Registry No.—2,2-Dimethyl-3-phenyl-1-propanol, 13351-61-6.

Reactions of Ethylene Di- and Trithiocarbonates with Acetylenes. Anomalous Reaction with Bromocyanoacetylene to Give a Thioacyl Bromide

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Received October 9, 1969

Most acetylenes having electron-withdrawing substituents react with O,S-ethylene dithiocarbonates or ethylene trithiocarbonates to give olefin and O,S-vinylene dithiocarbonates or vinylene trithiocarbonates. Bromocyanoacetylene does not eliminate ethylene from ethylene trithiocarbonate, but gives intensely colored, resonance-stabilized α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetyl bromide (**9**); **9** reacts with alcohols and amines to give thiono esters and thioamides.

In 1965, Easton and Leaver reported that dimethyl acetylenedicarboxylate reacts with ethylene trithiocarbonate (**1**) at 140° to give ethylene and 1,3-dithiole-2-thione (1,3-trithione) derivative **2a**.[1] Other five-membered-ring heterocycles which give cycloaddition–ring-opening reactions with acetylenes include 1,2-trithiones,[1-5] aza 1,2- and 1,3-trithiones,[6-8] and sydnones.[9] A similar reaction of N-sulfinylanilines with ethylene carbonate was reported.[10]

This paper describes further studies of the reactions of ethylene di- and trithiocarbonates with acetylenes.

Normal Reaction of Ethylene Trithiocarbonate (1).—Several acetylenes having electron-withdrawing groups reacted smoothly with **1** to give substituted 1,3-dithiole-2-thiones **2a–c**. The reactions proceeded at

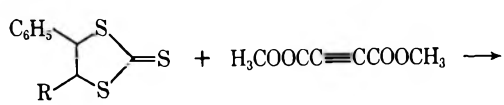
1

2a, R, R′ = $COOCH_3$
b, R, R′ = CF_3
c, R = CN; R′ = H
d, R, R′ = H

useful rates at 110–145°; yields were good. However, acetylene reacted with **1** only under forcing conditions to give **2d** in 2–5% yield; the product was grossly contaminated with tar. **1** did not react with methyl-, phenyl-, or diphenylacetylenes at 130–150°. At higher temperatures (180–190°) tar was formed, and no ethylene was detected. Thus, the scope of the reaction appears to be limited to negatively substituted acetylenes, with acetylene as a limiting case.

The structures of compounds **2b** and **2d** were established by comparison with published data and were further substantiated by single-line ^1H or ^{19}F nmr spectra, which virtually eliminate the isomeric 1,2-dithiolane-3-thione structures as possibilities. The structure of **2c** was assigned by analogy and was substantiated by spectral similarities to **2b** and **2d**.

Normal Reactions of Phenyl- and *cis*-Diphenylethylene Trithiocarbonates (3a and 3b).—In nmr-tube experiments, **3a**[11] was shown to react smoothly with dimethyl acetylenedicarboxylate at 88–90° to give **2a** and styrene. The reaction appeared to follow second-order kinetics in $CDCl_3$ solution. It was about 40% complete in 55 min and 72% complete in 220 min using equimolar quantities. A small solvent effect was detected; in $(CD_3)_2SO$ solution at 89–90°, the reaction was about 35% complete in 27 min and 88% complete in 220 min.



3a, R = H
b, R = C_6H_5, *cis*

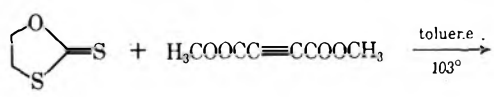
2a + $RCH{=}CHC_6H_5$

cis and *trans*

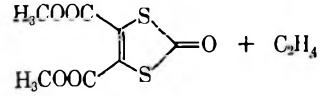
Similarly, **3b**[12] reacted with dimethyl acetylenedicarboxylate, the reaction being 31% complete in 1.0 hr at 78°. The products were **2a** and an apparent mixture of *cis*- and *trans*-stilbenes.

These results indicate that substitution of phenyl for H in **1** promotes the cycloaddition–ring-opening reaction moderately. However, the effect is apparently insufficient to enlarge the scope of the reaction appreciably. Neither **3a** nor **3b** reacted detectably with phenylacetylene at temperatures up to 160°.

Treatment of Dithiocarbonates with Acetylenes.—O,S-Ethylene dithiocarbonate[13] (**4**) reacted slowly with dimethyl acetylenedicarboxylate at 100° to give known compound **5**, whose structure was established by its spectra and by comparison with published data.[14]



4



5

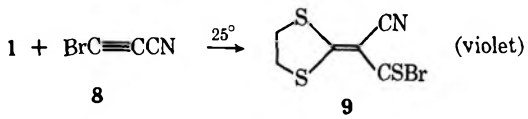
However, S,S′-ethylene dithiocarbonate (**6**) did not react with dimethyl acetylenedicarboxylate at 110° or 160°, and O,O′-ethylene thiocarbonate[13] (**7**) did not

(1) D. B. J. Easton and D. Leaver, *Chem. Commun.*, 585 (1965).
(2) H. Behringer and R. Widenmann, *Tetrahedron Lett.*, 3705 (1965).
(3) H. Behringer, J. Kilger, and R. Widenmann, *ibid.*, 1185 (1968).
(4) J. Vialle, *et al.*, *Bull. Soc. Chem. Fr.*, 1150, 3187 (1966).
(5) R. Mayer, H. J. Hartmann, and J. Jentzsch, *J. Prakt. Chem.*, **31**, 312 (1966).
(6) H. Behringer and D. Deichmann, *Tetrahedron Lett.*, 1013 (1967).
(7) D. Noel and J. Vialle, *Bull. Soc. Chim. Fr.*, 2239 (1966).
(8) H. Behringer, D. Bender, J. Falkenberg, and R. Widenmann, *Chem. Ber.*, **101**, 1428 (1968).
(9) R. Huisgen, German Patent 1,261,124 (1968), to Farbwerke Hoechst Aktiengesellschaft.
(10) O. Tsuge, M. Tashiro, and F. Mashiba, *Bull. Chem. Soc. Jap.*, **40**, 2709 (1967).
(11) H. A. Stansbury, J. A. Durden, Jr., and W. H. Catlett, Canadian Patent 682,545 (1964), example 5.
(12) C. G. Overberger and A. Drucker, *J. Org. Chem.*, **29**, 360 (1964).
(13) F. N. Jones and S. Andreades, *ibid.*, **34**, 3011 (1969).
(14) R. Mayer and B. Gebhardt, *Chem. Ber.*, **97**, 1298 (1964).

react at 80°, its upper limit of stability. Evidently, this reaction is characteristic of substrates having the -C(=S)S- configuration.

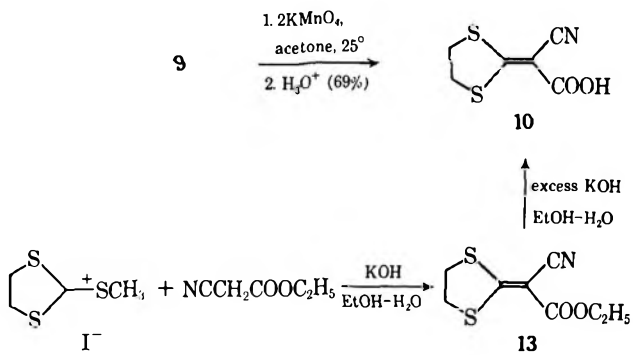
Part of the driving force for the reaction of **4** is probably the conversion of a thionocarbonate to a thiolcarbonate. Bond energy data indicate that this process is exothermic by 24 kcal/mol in simple systems.[15]

Anomalous Reaction of 1 with Bromocyanoacetylene (8).—When **1** and **8**[16] were mixed in benzene, a mildly exothermic reaction occurred and, after a few hours, a good yield of 1:1 adduct was obtained as brilliant violet crystals. No ethylene was evolved. The adduct fumed in a humid atmosphere, but it could be handled in dry air.



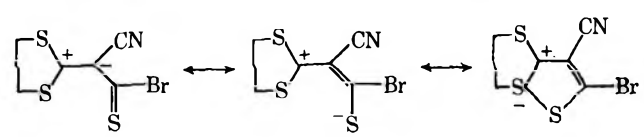
8 9

This adduct was assigned structure **9**, α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetyl bromide, primarily on the basis of its conversion to derivative **10** which was prepared independently by an established route.[17]



The structure of **9** was substantiated by spectral data. The nmr spectrum in CH_2Cl_2 appeared as a symmetrical pentuplet centered at δ 3.68. The infrared spectrum had a nitrile band at 2200 cm^{-1} and very strong bands at 1355 and 1325 cm^{-1}.

The absence of absorption in the normal double-bond region of the infrared spectrum of **9** and the presence of very strong bonds at 1355 and 1325 cm^{-1} suggest that resonance structures **9a**, **9b**, and **9c** may contribute significantly to the resonance hybrid. The intense color also suggests a resonance hybrid with charge separation.



9a 9b 9c

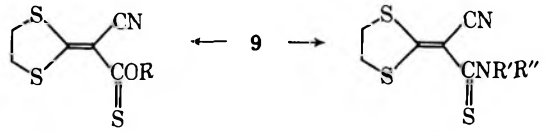
Compound **9** is believed to be the first example of a stable thioacyl bromide, although thioacyl fluorides and chlorides are well known. Its stability probably results from the unusual degree of electron delocalization.

(15) E. S. Kooyman in "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, Chapter 1.

(16) E. Kloster-Jensen, *Acta Chem. Scand.*, **17**, 1859 (1963); **17**, 1862 (1963); **18**, 1629 (1964).

(17) R. Mayer and K. Schafer, *J. Prakt. Chem.*, **26**, 279 (1964).

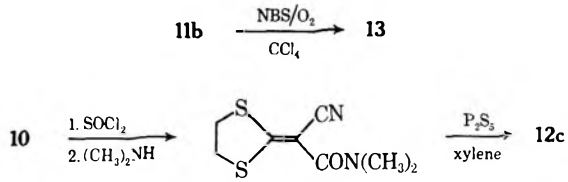
Compound **9** reacts readily with amines and alcohols to form yellow thiono esters **11a** and **b** and thioamides **12a–d**.



11a, R = CH_3 (95%)
b, R = C_2H_5 (85%)

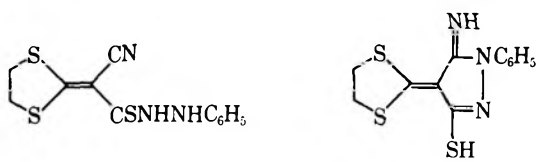
12a, R' = CH_3; R" = H (96%)
b, R' = C_2H_5; R" = H (95%)
c, R', R" = CH_3 (98%)
d, R', R" = C_2H_5 (78%)

The structures of **11** and **12** were established by conversion of thiono ester **11b** to known ester **13** by treatment with N-bromosuccinimide in air and by independent synthesis of thioamide **12c**.



Spectral data also supported the assigned structures. The nmr spectrum of ethanol adduct **11b** in $CDCl_3$ had, in addition to the triplet–quartet pattern of the ethyl protons, a broadened singlet at δ 3.63 (4 H) which at higher resolution appeared as a symmetrical pentuplet. The infrared spectrum had a nitrile band at 2200 cm^{-1} and a strong band at 1445 cm^{-1}. The absence of a strong peak assignable to C=O showed that the ester had the less stable thiocarbonyl structure. The electronic spectrum in CH_3CN had maxima at 246 mμ (ε 12,000), 278 (4350), 300 (5400), and 360 (18,400). Spectra of **11a** and of **12a–d** (see Experimental Section) were consistent with the assigned structures.

Phenylhydrazine reacted with **9** at 25° to give a red-brown solid, mp 235–236° dec, which had no nitrile absorption in the infrared spectrum. Probably the product is not **14** but some product of further reaction such as **15**.



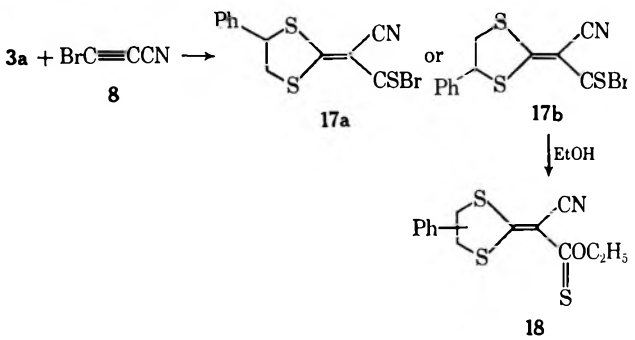
14 15

Thioacetyl bromide (**9**) reacted with potassium fluoride in refluxing acetonitrile to give the corresponding thioacyl fluoride, **16**, similar in color to **9**. The structure was strongly supported by analytical and spectral data. The ^{19}F nmr spectrum had a sharp singlet at −110.2 ppm from $Cl_2FCCFCl_2$; thioacyl fluorides are reported to have resonances between −107 and −162 ppm from $Cl_2FCCFCl_2$.[18]

Treatment of phenylethylene trithiocarbonate (**3a**) with **8** at 25° also gave a red-violet solid for which ana-

(18) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Org. Chem.*, **30**, 1375 (1965).

lytical and spectral data support structure **17a** or **17b**. This thioacetyl bromide was converted into the ethyl thiono ester **18**.



The mechanisms of these reactions have not been studied in detail. The fact that dithionocarbonate **4** reacts to give **5** and that **6** and **7** do not react strongly suggests that the exocyclic sulfur of ethylene trithiocarbonates becomes endocyclic during the normal reaction. Mechanisms in which the two ring sulfur atoms are incorporated in the ring of the final product seem to be eliminated. The anomalous reaction of bromocyanoacetylene (**8**) occurs at lower temperatures, indicating that a lower energy pathway available to **1** and **8** supersedes the normal reaction.

Experimental Section[19]

Dimethyl 2-Thiono-1,3-dithiole-4,5-dicarboxylate (**2a**).—A mixture of 27.4 g (0.20 mol) of ethylene trithiocarbonate (**1**), 28.5 g (0.20 mol) of dimethyl acetylenedicarboxylate, and 100 ml of toluene was heated at reflux for 4 hr. Pentane was slowly added to precipitate **2a**. Recrystallization from toluene–pentane gave 26.3 g (53%) of yellow dithiolane **2a**: mp 72–72.5°; ir (KBr) 1721, 1742 cm^{-1}; nmr ($CDCl_3$) δ 3.88. Use of refluxing xylene as solvent gave dark colored **2a**, mp 69–70.5°, in 33% yield.

Anal. Calcd for $C_7H_6O_4S_3$: C, 33.59; H, 2.42; S, 38.51. Found: C, 33.99; H, 2.53; S, 38.70.

4,5-Bis(trifluoromethyl)-1,3-dithiole-2-thione (**2b**).—A mixture of 34 g (0.25 mol) of **1**, 49 g (0.3 mol) of hexafluoro-2-butyne, and 60 g of toluene was heated in a steel pressure tube at 120° for 3 hr and at 160° for 3 hr. Fractionation through a spinning-band column gave 51 g (76%) of pale orange **2b**, bp 186–187°; the product was identical with the material obtained from hexafluoro-2-butyne, sulfur, and CS_2:[20] ir (neat) 1555, 1270, 1250, 1170, 925, 895 cm^{-1}.

2-Thiono-1,3-dithiole-4-carbonitrile (**2c**).—A solution of 5.9 g (0.043 mol) of **1** and 2.5 g (0.05 mol) of cyanoacetylene in 100 ml of xylene was stirred at 25° for several hours; no gas was evolved. The solution was refluxed for 20 hr, the temperature rose gradually from 120 to 135°, and 0.5 l. of water-insoluble gas evolved. The mixture was cooled and 3.0 g (0.06 mol) of cyanoacetylene was added. After 10 hr of further refluxing, the temperature was 130°, 1.75 l. (*ca.* 0.07 mol) of gas had evolved, and the rate of gas evolution was very slow. The dark red reaction mixture was concentrated under nitrogen, and the semisolid residue was extracted with three 200-ml portions of hot hexane–benzene (98:2). Cooling the extracts gave 2.1 g (33%) of yellow-bronze **2c**, mp 92.5–96°. Recrystallization followed by sublimation at 90° (0.2 mm) gave yellow **2c**: mp 100–101.5°; ir ($CHCl_3$) 3080 (w), 2980 (w), 2210 (m), 1100 (m), 1070 (vs), 872 (m), 840 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.78 (s).

Anal. Calcd for C_4HNS_3: C, 30.16; H, 0.63; N, 8.80. Found: C, 30.04; H, 0.59; N, 8.63.

1,3-Dithiole-2-thione (**2d**).—A mixture of 34.1 g (0.25 mol) of **1**, 80 g of acetone, and 26 g (1 mol) of acetylene was agitated in a 240-ml stainless steel tube (barricade) at 150° for 4 hr and then at 200° for 4 hr. The resulting red solution was concentrated to give 33.8 g of red oil which was estimated by nmr analysis to contain 5–6% **2d** and much unreacted **1**. Repeated extraction with pentane gave 0.4 g of residual **2d**, an impure oil having all the ir and nmr [δ 7.18 ($CDCl_3$)] peaks of **2d** independently synthesized by the method of Mayer.[14]

Reactions of Phenyl and *cis*-Diphenyl Trithiocarbonates with Dimethyl Acetylenedicarboxylate.—These reactions were effected by immersing solutions of reagents in nmr tubes in a thermostatically controlled oil bath. After the indicated time, the tubes were quickly cooled. The compositions of the resulting solutions were estimated by comparison of their nmr spectra with those of starting materials and products.

Dimethyl 2-Oxo-1,3-dithiole-4,5-dicarboxylate (**5**).—A solution of 3.6 g (0.03 mol) of yellow O,S-ethylene dithiocarbonate[13] (**4**) and 4.2 g (0.03 mol) of dimethyl acetylenedicarboxylate in 30 ml of toluene was heated at 103° in the dark for 6 hr and kept at 25° for 3 days. The red solution was concentrated to give 6.9 g of oil whose ir spectrum showed substantial amounts of unreacted starting materials. Fractional recrystallization from methylene chloride and from methanol followed by sublimation gave 2.4 g (34%) of colorless **5**, mp 66–67° and 65.5–67° (lit.[14] mp 70°).

Anal. Calcd for $C_7H_6O_5S_2$: C, 35.89; H, 2.58; S, 27.37. Found: C, 36.02; H, 2.71; S, 27.23.

α-Cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetyl Bromide (**9**).—A solution of 25 g (0.19 mol) of bromocyanoacetylene[16] and 27 g (0.20 mol) of ethylene trithiocarbonate (**1**) in 400 ml of benzene was stirred at 25–30° for 24 hr; 43 g (83%) of purple-red **9**, mp 120–124° dec, was collected. Recrystallization of 1.0 g from 25 ml of benzene yielded 0.5 g of brilliant purple needles: mp 126° dec; ir (KBr) 3000 (w), 2200 (m), 1355, 1325 (s), 1275 (m), 1245 (m), 1155 (m), 1045 (w), 953 (m), 930 (w), 840 (w) cm^{-1}; nmr (CH_2Cl_2) δ 3.68 (broadened singlet) (at 50-cps sweep width the spectrum appeared to be a symmetrical quintet centered at δ 3.68 with a 7.6-Hz separation between the weak outer wings); uv–vis (CH_3CN) λ_{max} 242 mμ (ϵ 20,000), 266 (6400), 294 (3300), 330 (3860), 400 (19,200), 520 (130).

Anal. Calcd for $C_6H_4BrNS_3$: C, 27.07; H, 1.52; N, 5.27; Br, 30.02; S, 36.13; mol wt, 266. Found: C, 27.16; H, 1.43; N, 5.27; Br, 30.10; S, 35.51; mol wt, 284 (cryoscopic, C_6H_6), 284 (vapor pressure osmometer, $CHCl_3$), 284 (ebullioscopic, CH_2Cl_2).

α-Cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-acetic Acid (**10**).—A solution of 12 g (0.0076 mol) of potassium permanganate in 1400 ml of acetone was added rapidly to a slurry of 8 g (0.03 mol) of **9** in 100 ml of acetone. The brown precipitate was collected and extracted thoroughly with dilute aqueous potassium hydroxide. Acidification with dilute sulfuric acid precipitated 3.8 g (67%) of **10**, mp 240–250° dec. Recrystallizations from 400 ml of acetonitrile (Darco) and from acetic acid gave pale yellow **10**: mp 228.5–230° (lit.[17] mp 248–249°); ir (KBr) 3300–2400 (br), 2205 (m), 1670 (s), 1455 (s), 1295–1280 (s), 1180 (m), 930 (w), 900 (w), 725 cm^{-1}; nmr (CD_3SOCD_3) δ 10.0 (s, 1), 3.77 (s, 4). These spectra were identical with those of acid **10** synthesized independently substantially as described.[17]

Anal. Calcd for $C_6H_5NO_2S_2$: C, 38.48; H, 2.70; N, 7.48; S, 34.25. Found: C, 38.26; H, 2.73; N, 7.49; S, 33.92.

O-Methyl α-Cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetate (**11a**).—A slurry of 2.6 g (0.01 mol) of **9** in 75 ml of methanol was stirred for 12 hr at 25°. Thionoester **11a** was collected as 2.1 g (95%) of light brown solid, mp 133–135° dec. Recrystallization from 70:30 benzene–hexane gave yellow **11a**, mp 135–138° dec.

Anal. Calcd for $C_7H_7NS_3O$: C, 38.68; H, 3.25; N, 6.45. Found: C, 38.38; H, 3.15; N, 6.46.

O-Ethyl α-Cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetate (**11b**).—This thiono ester, mp 133–134° dec, was prepared similarly, in 85% yield, from **9** and ethanol.

Anal. Calcd for $C_8H_9NOS_3$: C, 41.52; H, 3.93; N, 6.06; S, 41.57. Found: C, 41.42; H, 3.94; N, 6.13; S, 41.88.

Conversion of 11b into Ethyl-α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-acetate (**13**).—A mixture of 9.2 g (0.04 mol) of thiono ester **11b** and 7.2 g (0.04 mol) of N-bromosuccinimide in 120 ml of carbon tetrachloride was refluxed in air for 20 hr. When filtered and cooled, the filtrate yielded 2.85 g (25%) of a yellow solid, mp 97–99°. Recrystallization of 1 g from 25 ml of 60:40 benzene–hexane (Darco) yielded 0.5 g of **13**: mp 102–103° (lit.[17] mp 104.5–105°); ir (KBr) 1700 cm^{-1}. This material was identical with **13** independently prepared by a known method.

(19) Melting points and boiling points are uncorrected. Infrared spectra were recorded linear in wavelength using a Perkin-Elmer Model 21 device. Nmr spectra were produced on Varian A-60, HR-100, and A-56/60 devices. Uv–visible spectra were recorded on a Cary Model 14 spectrophotometer.

(20) C. G. Krespan and D. C. England, *J. Org. Chem.*, **33**, 1850 (1968).

Anal. Calcd for $C_8H_9NS_2O_2$: C, 44.63; H, 4.21; N, 6.51; S, 29.79. Found: C, 44.75; H, 4.17; N, 6.54; S, 30.03.

N-Methyl-α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetamide (12a).—Anhydrous methylamine was bubbled through a stirred solution of 5.3 g (0.02 mol) of **9** in 125 ml of tetrahydrofuran until the red color discharged. The precipitate was collected (3.82 g). Extraction with 40 ml of distilled water left 1.63 g of yellow, insoluble **12a**, mp 218–220°. The tetrahydrofuran solution was concentrated to give 2.6 g of **12a**, mp 198–212°. Recrystallization from benzene (110 ml/g) gave yellow **12a**: mp 219–221°; ir (KBr) 3300 (m), sharp, 2910 (w), 2200 (m), 1535 (m), 1480 (s), 1425 (m), 1345 (m), 1275 (m), 1245 (m), 1058 (m), 990 (w), 920 (w), 790 (w), 683 (w), cm^{-1}; nmr (CD_3SOCD_3) δ 8.45 (br, 1), 3.72 (s, 4), 3.12 (d, 3, J = 4.5 Hz).

Anal. Calcd for $C_7H_8N_2S_3$: C, 38.84; H, 3.73; N, 12.94; S, 44.46, mol wt, 216. Found: C, 38.76; H, 3.92; N, 12.97; S, 44.54; mol wt, 209 (cryoscopic, Me_2SO).

N-Phenyl-α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetamide (12b).—A mixture of 5.3 g (0.02 mol) of **9**, 5.5 g (0.061 mol) of aniline, and 100 ml of tetrahydrofuran was stirred for several hours. Aniline hydrobromide (3.4 g, mp 260–280° dec) was filtered. The filtrate was concentrated under nitrogen to yield 5.5 g (95%) of **12b**, mp 153–160°. Two recrystallizations from benzene (*ca.* 1 g/50 ml of benzene) yielded bright yellow **12b**: mp 172.5–174.5°; uv–vis (CH_3CN) λ_{max} 243 mμ (ε 17,250), 292 (8400), 342 (17,400), 435 (sh) (550); ir and nmr comparable with those of **12a**.

Anal. Calcd for $C_{12}H_{10}N_2S_3$: C, 51.77; H, 3.63; N, 10.05. Found: C, 51.93; H, 3.47; N, 10.07.

N,N-Dimethyl-α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetamide (12c).—Tetrahydrofuran-soluble thioamide **12c** was prepared essentially as described for the preparation of **12a** and isolated in 98% yield as described for **12b**. Recrystallization from 70:30 benzene–hexane yielded bright yellow needles of **12c**, mp 146–148°; spectra were comparable with those of **12a** and **12b**.

Anal. Calcd for $C_8H_{10}N_2S_3$: C, 41.66; H, 4.37; N, 12.16; S, 41.75; mol wt, 230. Found: C, 41.51; H, 4.54; N, 12.17; S, 41.81; mol wt, 233 (cryoscopic, Me_2SO).

Independent Synthesis of 12b from 10.—**10** (4.7 g, 0.025 mol) was treated with excess thionyl chloride at reflux for 2 hr. After removal of volatiles, the crude acid chloride was treated with dimethylamine in tetrahydrofuran. The amide was isolated as described above for **12b**. Recrystallization from 60:40 hexane–benzene gave N,N-dimethyl-α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-acetamide, mp 69–70°.

Anal. Calcd for $C_8H_{10}N_2OS_2$: C, 44.85; H, 4.71; N, 13.07. Found: C, 44.80; H, 4.45; N, 12.95.

A mixture of 1.0 g (0.0047 mol) of this amide, 0.9 g (0.004 mol) of phosphorus pentasulfide, and 25 ml of xylene was heated on a steam bath for 4 hr. The xylene solution was decanted, and the oily residue was extracted with hot xylene. The xylene solution and extract were concentrated under nitrogen to yield 0.5 g of a yellow-orange solid, mp 60–140°. Crystallization from 50:50 hexane–benzene gave 0.025 g (25%) of bright yellow **12c**, mp 144.5–146.5°. The mixture melting point with **12c** obtained from **9** and dimethylamine was 144.5–146.5°. Ir spectra were identical.

N,N-Diethyl-α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetamide (12d).—This thioamide, mp 65–69°, was prepared essentially as described for **12b**. Recrystallization of 2.0 g from 100 ml of 50:50 ether–benzene (Darco treatment) yielded 0.6 g of an analytical sample, mp 66–68°. Spectra were comparable with those of **12a–c**.

Anal. Calcd for $C_{10}H_{14}N_2S_3$: C, 46.47; H, 5.46; N, 10.84. Found: C, 46.33; H, 5.40; N, 10.91.

Reaction of 9 with Phenylhydrazine.—The reaction was effected as described for preparation of **12b**, and the product, sparingly soluble in tetrahydrofuran, was isolated as described for **12a**. The maroon solid had mp 230–250° dec and 213–222° dec. Recrystallization of 1.0 g of the crude product from 100 ml of acetonitrile yielded 0.7 g of shiny red-brown plates tentatively assigned structure **16**: mp 235–236° dec; ir (KBr) 3300 (w), 3180 (w), 2315 (vw), 1640 (m), 1600 (w), 1560 (m), 1480 (s), 1435 (m), 1362, 1285 (m), 1245 (m), 918 (m), 782 (m), 763 (s), 695 (m) cm^{-1}; nmr (CD_3SOCD_3) δ 8.12 (m, 2), 7.51 (m, 3), 6.05 (br s, 2), 3.79 (q, 4, resolved only at 100 MHz); uv–vis (CH_3CN) λ_{max} 230 mμ (ε 18,750), 285 (15,100), 326 (20,200), 485 (3100).

Anal. Calcd for $C_{12}H_{11}N_3S_3$: C, 49.12; H, 3.78; N, 14.32; S, 32.83; mol wt, 293. Found: C, 49.23; H, 3.71; N, 14.27; S, 33.00; mol wt, 283 (cryoscopic Me_2SO).

α-Cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetyl Fluoride (15).—A mixture of 10.5 g (0.04 mol) of **9**, 25 g (0.40 mol) of anhydrous potassium fluoride, and 200 ml of acetonitrile was refluxed under nitrogen for 12 hr. The solids were filtered and washed with acetonitrile. The solutions were concentrated to give 6.9 g of crude **15**, mp 85–101°. Sublimation at 90° (0.05 mm) gave **15**: mp 105.5–107°; ir (KBr) 2995 (w), 2205 (m), 1775 (w), 1420 (s), 1355 (s), 1290 (m), 1248 (m), 1155 (m), 1120 (s), 1048 (m), 1000 (w), 968 (w), and 825 (s) cm^{-1}; uv–vis (CH_3CN), λ_{max} 219 mμ (ε 9300), 241 (11,600), 260 (sh) (4750), 317 (5550), 383 (18,200).

Anal. Calcd for $C_6H_4NS_3F$: C, 35.10; H, 1.97; N, 6.82; F, 9.25. Found: C, 35.16; H, 2.04; N, 7.02; F, 9.35.

***cis-* or *trans*-α-Cyano-4-phenyl-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetyl Bromide (17a or 17b).**—This product was prepared from **3a** and bromocyanoacetylene as described for preparation of **9**. The initial precipitate (60% yield, mp 125–126° dec) was recrystallized from 50:50 hexane–benzene to give red-violet **17a** or **17b**: mp 125–126°; ir (KBr) 3000 (w), 2205 (m), 1390 (s), 1308 (s), 950 (m), 735 (m), 695 (m), cm^{-1}; nmr ($CDCl_3$) δ 8.5 (s, 5), 5.38 (t, 1), 3.81–4.05 (m, 2); uv–vis (CH_3CN) λ_{max} 244 mμ (ε 24,700), 265 (sh), 295 (3750), 334 (3860), 408 (20,150), 522 mμ (126).

Anal. Calcd for $C_{12}H_8NS_3Br$: C, 42.10; H, 2.36; N, 4.09; Br, 23.35; S, 28.11; mol wt, 342. Found: C, 42.16; H, 2.21; N, 3.85; Br, 23.32; S, 28.20; mol wt, 347 (freezing point, C_6H_6).

***cis-* or *trans*-O-Ethyl-α-cyano-4-phenyl-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetate.**—A slurry of 1.0 g (2.9 mol) of **17a** or **17b** in 30 ml of ethanol was stirred overnight at 25° to give 0.6 g (60%) of the thiono ester: mp 133–134° without purification; ir (KBr) 3000 (w), 2202 (m), 1455 (s), 1305 (s), 1240 (s), 1108 (m), 1035 (m), 970 (m), 768 (m), 695 (m), cm^{-1}; nmr ($CDCl_3$) δ 8.42, (br, s, 5), 5.18 (t, 1, J = 8.5 Hz), 4.57 (q, 4, J = 7 Hz); uv–vis (CH_3CN) λ_{max} 247 mμ (ε 16,300), 305 (5500), 363 (19,000).

Anal. Calcd for $C_{14}H_{13}NOS_3$: C, 54.66; H, 4.26; N, 4.56; S, 31.28. Found: C, 54.82; H, 3.94; N, 4.51; S, 31.64.

Registry No.—**2a**, 7396-41-0; **2b**, 16005-62-2; **2c**, 24058-51-3; **9**, 24058-52-4; **10**, 2080-63-9; **11a**, 24058-54-6; **11b**, 24058-55-7; **12a**, 24058-56-8; **12b**, 24118-55-6; **12c**, 24058-57-9; **12d**, 24058-58-0; **15**, 24118-56-7; **16**, 24058-59-1; **17a**, 24058-34-2; **17b**, 24058-35-3; N,N-dimethyl-α-cyano-1,3-dithiolane-$\Delta^{2,\alpha}$-acetamide, 24058-60-4; *cis*-O-ethyl-α-cyano-4-phenyl-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetate, 24058-36-4; *trans*-O-ethyl-α-cyano-4-phenyl-1,3-dithiolane-$\Delta^{2,\alpha}$-thioacetate, 24058-37-5; bromocyanoacetylene, 3114-46-3.

Nucleophilic Substitution at Dicoordinated Sulfur. Effect of the Leaving Group on the Reaction between Triphenylmethyl Sulfenyl Derivatives and *n*-Butylamine

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The rates of reaction between trityl sulfenyl chloride, bromide, iodide, thiocyanate, and *n*-butylamine have been measured in benzene and in benzene–ethanol (1:1) at 25° by a spectrophotometric technique. In solvent benzene, for all substrates the rate depends on the square of the amine concentration, while in benzene–ethanol the reactions are first order in amine. The change in leaving group does not cause large variations in the reaction rates. The relative rates for nucleophilic displacement at dicoordinated sulfur with I, SCN, Br, and Cl, respectively, as leaving groups are the following: (a) in benzene, 1, 3, 190, and 140; (b) in benzene–ethanol, 1, 2.2, 191, and 400. Such an order of relative rates is discussed in terms of sulfur d-orbital participation in the transition state.

The question of d-orbital participation in nucleophilic substitution at sulfenyl sulfur was discussed by Parker and Kharasch in 1959.[1] Since then only a few articles have appeared dealing with the same subject. The view originally expressed by Fava and Iliceto[2] that there is little if any d-orbital participation to the transition state is supported by more recent papers[3] and by some unpublished data.[4] However, evidence for the formation of pentacoordinate sulfur compounds as intermediates in organic reactions has been reported by Kwart[3a] for the chlorination of sulfenyl chlorides and by Trost[6] in the reaction of sulfonium salts with organolithium compounds.

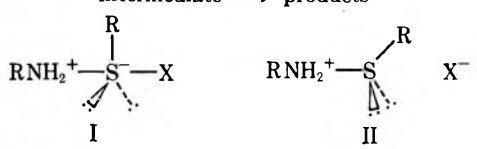
In a recent paper[7] we have already taken up this problem by studying the reaction between triphenylmethyl sulfenyl chloride (RSCl) and *n*-butylamine ($BuNH_2$) to form N-(*n*-butyl)-triphenylmethyl sulfenamide (RSNHBu) and *n*-butylamine hydrochloride (eq 1, X = Cl).

$$RSX + 2BuNH_2 \longrightarrow RSNHBu + BuNH_3X \qquad (1)$$

In benzene the reaction is cleanly second order in amine while in the presence of several additives a term which is first order in amine is also important and in some cases predominates. Consideration of the effect of the additives led to the conclusion that the reaction is subject to general base catalysis. A two-step mechanism (2a,b), where hydrogen abstraction occurs after formation of an intermediate, has been postulated. Although we were inclined to consider more likely the formation of a pentacovalent intermediate (I),

$$RSX + BuNH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \qquad (2a)$$

$$\text{intermediate} \xrightarrow{k_B[B]} \text{products} \qquad (2b)$$



formed through the use of sulfur d orbitals, we could not rule out an ion-pair intermediate (II). We felt that a more conclusive answer about which of the two intermediates is formed and about the general problem of d-orbital participation in nucleophilic substitution at divalent sulfur could be offered by a study of the leaving group effect on reaction 1 since such an effect is related to the amount of bond breaking at the transition state.

Results

The rates of reaction of triphenylmethyl sulfenyl bromide, RSBr, triphenylmethyl sulfenyl iodide, RSI, and triphenylmethyl sulfenyl thiocyanate, RSSCN, with $BuNH_2$ have been measured in benzene at 25°. In all cases the sulfenamide and the corresponding *n*-butylammonium salt were formed (eq 1) in quantitative yield. The data are collected in Table I. The general behavior of these substrates is very similar to that already found for RSCl.[7] The pseudo-second-order rate coefficient, $k_2 = k'/[BuNH_2]$, where k' is the pseudo-first-order rate coefficient, varies linearly with the amine concentration (eq 3) and vanishes at zero

$$k_2 = k_3[BuNH_2] \qquad (3)$$

amine concentration, as shown in Figure 1. Thus for all substrates in benzene the reaction is second order in amine. Since the salt formed in the reaction is a good catalyst, at low amine concentration autocatalysis was observed; thus initial rates have been measured. As the concentration of amine is increased, the catalytic effect of the salt becomes negligible and the pseudo-first-order plots appear to be linear within experimental error. This phenomenon has been considered in detail in the preceding paper[7] for RSCl and we shall not discuss it further. The close similarity of behavior between RSCl and the substrates considered in this paper is also shown by their response to additions of salts, polar solvents, or tertiary amines.[8] It is this similarity between the various substrates, which implies an identity of mechanism under various experimental conditions, which will allow us to draw meaningful conclusions from their relative rates of reaction.

As seen for RSCl,[7] one of the important consequences of the presence of additives is that in their presence the second-order rate constant, k_2, still varies linearly with

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(2) A. Fava and A. Iliceto, *J. Amer. Chem. Soc.*, **80**, 3478 (1958).
(3) (a) E. N. Givens and H. Kwart, *ibid.*, **90**, 378, 386 (1968); (b) J. L. Kice and J. M. Anderson, *J. Org. Chem.*, **33**, 3331 (1968); (c) C. Brown and D. R. Hogg, *Chem. Commun.*, 38 (1967).
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(8) E. Ciuffarin and G. Guaraldi, unpublished results.

TABLE I

KINETIC DATA FOR THE REACTION BETWEEN RSX AND $BuNH_2$ IN BENZENE AT 25°

RSX[a]	$[BuNH_2] \times 10^2$ M	$k' \times 10^4$ sec^{-1}	$k_2 \times 10^3$ M^{-1} sec^{-1}
X = Br	0.256	0.26[b]	10.1
	0.508	1.1[b]	22
	0.566	1.1[b,c]	20
	0.968	3.6[b]	37
	1.00	3.7[b]	37
	1.13	4.3[b,c]	38
	2.26	18[c]	79
	2.31	19	82
	2.56	26	100
	4.29	59	140
	5.08	91	180
X = I	4.52[d]	0.44[b,d]	0.98
	5.08	≤0.48[b,e]	≤0.95
	5.08	0.41[b]	0.81
	6.71	0.63[b]	0.94
	9.05	1.7[b,d]	1.9
	10.0	1.9[b]	1.9
	16.6	5.6[b]	3.4
	18.1[d]	5.7[b,d]	3.1
	19.4	5.8	3.0
	32.7	24	7.3
X = SCN	5.08	1.3	2.6
	13.2	8.6[b]	6.5
	33.1	61	18

[a] The concentration of the substrate ranged between 1 and 2 × 10^{-4} M. [b] Initial rate. [c] In the presence of 73 mg/l. of decomposition products (see Results). [d] In the presence of 79 mg/l. of decomposition products (see Results). [e] [RSI] = 2.9 × 10^{-2} M; followed by titration with iodate (see Experimental Section).

the amine concentration but a term which is first-order in amine emerges (eq 4). The form of eq 4 shows that

$$k_2 = k_0 + k_3'[BuNH_2] \quad (4)$$

the effect of the leaving group cannot be drawn directly from a comparison of the second-order rate constant, k_2, which is not independent of the amine concentration. The effect of the leaving group can be measured on k_0 and/or k_3 which are both independent of the amine concentration. The data in benzene are perfectly suited to measure the effect of the leaving group on k_3 since in such a solvent eq 3 applies. To determine the leaving-group effect on k_0 a solvent medium has to be found where the third-order term ($k_3'[BuNH_2]$) is negligible and thus $k_2 = k_0$. A suitable solvent is a 50% benzene–alcohol mixture,[9] where k_2 is in fact independent of the amine concentration. The data are collected in Table II.

Although ethyl alcohol reacts with sulfenyl halides,[10] experiments showed that the reaction is very much slower than that which occurs upon further addition of $BuNH_2$. Moreover, the only product recovered in quantitative yield from the sulfenyl derivatives (0.2 M) and $BuNH_2$ (0.4 M) in 50% benzene–ethanol was the sulfenamide. Although product identification could not be performed under the highly diluted kinetic conditions, the possibility of ethanolysis in the kinetic runs was excluded on mechanistic grounds. Ethanolysis is in fact very slow also in the presence of a large excess of triethylamine (3.36 × 10^{-2} M), while 2.58 × 10^{-3} M

(9) In pure ethyl alcohol the reaction is too fast to be measured with standard techniques for RSCl and RSBr.

(10) L. Goodman and N. Kharasch, *J. Amer. Chem. Soc.*, **77**, 6541 (1955).

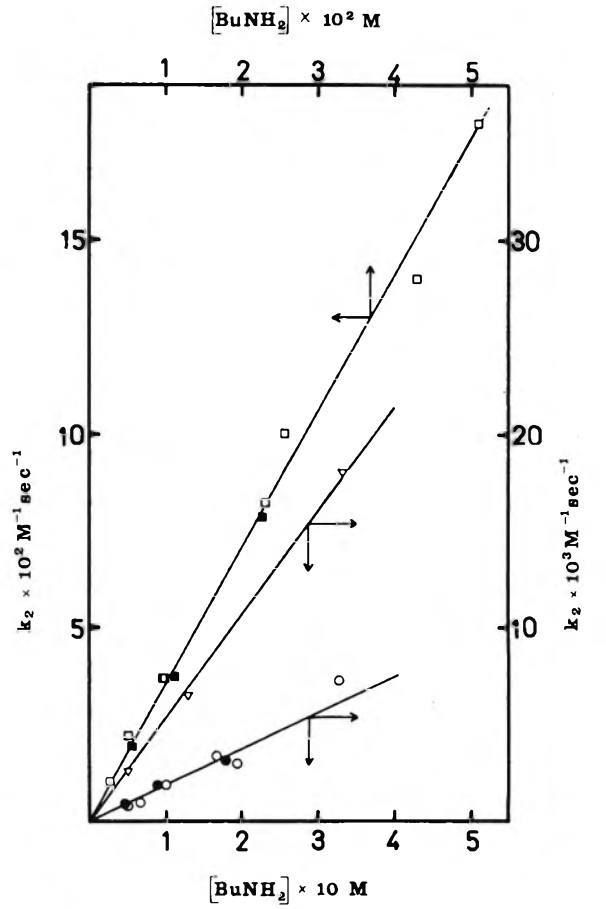

Figure 1.—Plots of the second-order rate constant for the reaction of *n*-$BuNH_2$ with RSX in benzene at 25° *vs.* the amine concentration: □ = RSBr, ▽ = RSSCN, ○ = RSI, ■ = RSBr in the presence of decomposition products, ● = RSI in the presence of decomposition products.

TABLE II

KINETIC DATA FOR THE REACTION BETWEEN RSX AND $BuNH_2$ IN 50% BENZENE–ETHANOL AT 25°

RSX[a]	$[BuNH_2] \times 10^3$ M	$k' \times 10^4$ sec^{-1}	k_2, M^{-1} sec^{-1}
X = Cl	2.76	190	6.9
	4.32	290	6.7
	2.58[b]	180	7.0
X = Br	2.76	91	3.3
	5.66[c]	180	3.2
X = SCN	1.44	0.56	0.039
	4.32	1.6	0.037
	27.6	10.5	0.038
X = I	27.6	4.7	0.017
	45.2[d]	7.7	0.017

[a] The substrates' concentration ranged between 1 and 2 × 10^{-4} M. [b] With added Et_3N, 3.36 × 10^{-2} M. [c] In the presence of 70 mg/l. of decomposition products (see Results). [d] In the presence of 85 mg/l. of decomposition products (see Results).

butylamine is sufficient to cause fast reaction. Thus, addition of ethyl alcohol does affect the reaction rate without changing the products. The rates and their relative values in pure benzene and in 50% benzene–ethanol are summarized in Table III.

Owing to their thermal lability RSBr and RSI could not be thoroughly purified and their elemental analysis was less than satisfactory. A purity of 96% could be approximately assessed for the two products. One could argue that the presence of impurities might affect in some way the kinetics and thus impair the results

TABLE III

SUMMARY OF THE LEAVING-GROUP EFFECT IN BENZENE AND 50% BENZENE–ETHANOL

X	k_2, M^{-1} sec^{-1}	Benzene, relative rates	—50% benzene-ethanol— k_2, M^{-1} sec^{-1}	Relative rates
Cl	2.6[a]	140	6.8[c]	400
Br	3.6[b]	190	3.25[c]	191
SCN	.057[b]	3	0.038[c]	2.2
I	.019[b]	1	0.017	1

[a] From ref 7. [b] Calculated from the slope of Figure 1. [c] Average value.

and the mechanistic conclusions resting on them. Hence, a number of experiments has been performed in the presence of a relatively large amount (about the same weight of the substrate) of their own decomposition products (see Experimental Section). The data thus obtained are identical within experimental error with those found without addition of decomposition products.

Discussion

The effect of the leaving group on the rate of reaction has long been recognized as a useful criterion for distinguishing whether or not bond breaking has made significant progress in the transition state.[11-13] If the leaving group is still almost fully bonded in the transition state, its electronegativity is the most important factor regulating the reactivity of the substrate;[11,14] on the contrary, when bond breaking is important, basicity of the leaving group and strength of the bond which is broken are responsible for the mobility of the group to be displaced,[15,16] bond strength being the more important factor.

Examples of reactions occurring with or without significant bond breaking in the transition state are well known for substitution at aliphatic, aromatic, or carbonyl carbon. When bond breaking is important, the halogen mobility follows the order I > Br > Cl with a Br/Cl ratio of about 400.[17] On the contrary, when bond breaking is unimportant, the difference in mobility is usually small[12,18] and mostly in the reverse order.

The effect of the leaving group has also been measured in nucleophilic substitutions at silicon[19] and sulfur.[4b,20] However, the difference in leaving group was obtained by a *para* substitution while maintaining constant the element displaced. Clearly in such cases the mobility of the leaving group parallels its basicity.

This is the first example of a study of the leaving group effect on sulfur obtained by a change of the displaced element.

Although to our knowledge no bond dissociation energies for the S–X bond of sulfenyl derivatives are available, data from organic and inorganic halides and sulfides[21] allow us to reasonably assess the following order of decreasing bond strength: S–Cl ≃ S–SCN > S–Br > S–I.

Were bond breaking important in nucleophilic displacement at divalent sulfur, we would expect the mobility of the leaving group to follow the order I > Br > SCN ≃ Cl. This order does not resemble the leaving group mobilities summarized in Table III. Chlorine is in fact at least 100 times more easily displaced than iodine; *i.e.*, the substrate with the weaker S–X bond reacts more slowly. Thus we do not expect appreciable S–X bond fission at the transition state.

In order to explain the second order in amine found in benzene, the mechanism involving the intermediate (eq 2) seems the most likely explanation.[7] The present results rule out an attack by an amine dimer even though such a possibility is sometimes offered as an explanation of the order 2 in amine.[22] A one-step nucleophilic displacement by an amine dimer would in fact assume appreciable S–X bond fission at the transition state and iodine should be much more easily displaced than chlorine. On the same grounds we can also exclude the possibility of an ionization mechanism *via* sulfenium ions (eq 5) which have been postulated for many reactions of sulfenyl derivatives.[23]

$$\mathrm{RSX} \underset{\text{assisted by additives}}{\rightleftharpoons} \mathrm{RS^+ + X^-} \xrightarrow{\mathrm{B}} \text{products} \qquad (5)$$

Steady-state treatment of eq 2 gives

$$k_2 = \frac{k_1 k_B[B]}{k_{-1} + k_B[B]} \qquad (6)$$

where k_2 is the observed second-order rate coefficient. If we assume that in benzene $k_{-1} \gg k_B[B]$, eq 6 simplifies to

$$k_2 = \frac{k_1 k_B[B]}{k_{-1}} \qquad (7)$$

which is equivalent to the observed rate expression (eq 3). On the other hand in 50% benzene–ethanol overall second-order kinetics is observed which is consistent with the suggested mechanism, if in that medium $k_B[B] > k_{-1}$. This is reasonable in view of the consideration that the solvent itself may operate as the base.[7] Thus in 50% benzene–ethanol k_2 measures the rate of formation of the intermediate (eq 8).

$$k_2 = k_1 \qquad (8)$$

Table III shows that the relative mobility in 50% benzene–ethanol is Cl > Br > SCN > I. This order parallels nicely the order of decreasing electronegativity of the group to be displaced. It seems that the major "effect" of the leaving group is that of creating a positive charge on the reaction center facilitating the rate of formation of the intermediate without extensive bond breaking. A very similar situation can be found in aromatic nucleophilic substitutions where the second

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(20) J. L. Kice and G. Guaraldi, *J. Org. Chem.*, **31**, 3568 (1966).
(21) T. L. Cottrell, "The Strength of Chemical Bonds," Butterworths, London, 1954.
(22) (a) F. M. Menger, *J. Amer. Chem. Soc.*, **88**, 3081 (1966); (b) R. F. Hudson and I. Stelzer, *J. Chem. Soc., B*, 775 (1966).
(23) N. Kharasch, "Organic Sulfur Compounds," Vol. 1, Pergamon Press, Oxford, 1961, pp 375–396.

step of the intermediate complex mechanism[11,18] is not rate determining. In these cases the maximum variation for different leaving groups goes from 5 to 100.[11,18]

In benzene a similar order of reactivity obtains even though the comparison involves third-order rate coefficients resulting from a combination of no less than three rate constants, $k_3 = k_1k_B/k_{-1}$ (eq 7). This may be taken to imply that the factor controlling the relative rate is again the formation of the intermediate.

Since in both solvent media bond breaking seems unlikely to occur to an appreciable extent, the only way to account for this is to assume that sulfur expands its valence shell and that the leaving group is still almost fully bonded in the transition state. In benzene–ethanol, once the transition state is passed, formation of products is very fast and no intermediate can be kinetically detected. In benzene, where hydrogen abstraction is the slow step, an intermediate is formed. This intermediate could either be an ion pair (II) or a complex where both entering and leaving groups are bonded to a pentacovalent sulfur (I). The formation of an ion pair has been suggested by Kharasch and Goodman[10] in the base-catalyzed methanolysis of sulfenyl halides and by Savige and Fava[24] in the base-catalyzed racemization of thiolsulfinates.

Although we cannot rule out the formation of an ion pair, we prefer the pentacovalent complex since the very labile intermediate is likely to be very close in energy and structure[25] to the pentacovalent transition state, from which it would differ only slightly in bond lengths. Its geometry is likely to be a trigonal bipyramid with the two electron pairs in radial position, as the most electropositive substituents, and with the amino and leaving groups in the apical positions as the more electronegative ligands[26] (I).

Very recently Kice and Anderson[3b] have taken a position against d-orbital participation in nucleophilic substitutions at sulfur. They support their view with other reported data[3a,c,4a] besides their own. Although we also tend to believe[4b] that in many instances there is no d-orbital participation, we would like to add a word of caution against generalizations. Even silicon, which is usually presented as an element which can easily expand its valence shell, does not always do so. There are data[3a,6] besides those presented in this paper that are certainly in favor of d-orbital participation. It might be the case that different charge distributions in the transition state could bring about structurally different transition states. As a matter of fact while d-orbital participation can be safely excluded with negatively charged nucleophiles, evidence in favor of d-orbital participation has been obtained when neutral reagents have been used.

Experimental Section

Materials.—Preparation and/or purification of benzene, *n*-butylamine, triphenylmethyl sulfenyl chloride, and N-(*n*-butyl)triphenylmethylsulfenamide have been already described.[7] Reagent grade absolute ethanol was used without further purification.

Triphenylmethyl Sulfenyl Bromide.—A suspension of 1 g of RSCl and 0.7 g of NaBr in acetone is vigorously stirred for about 1 hr.[27] The mixture is filtered and, after evaporation of the solvent in a rotary evaporator at room temperature, 0.9 g of crude RSBr is obtained. The crude bromide is dissolved in benzene, dried over anhydrous sodium sulfate, and filtered; the solution is concentrated in a rotary evaporator. Upon addition of petroleum ether (bp 40–60°) a precipitate obtains which is further recrystallized from benzene–petroleum ether, yield 50%, orange crystals which slowly decompose at room temperature or faster upon heating. The product can be kept for extended periods at temperatures below 0°.

Anal. Calcd for $C_{19}H_{15}SBr$: C, 64.25; H, 4.22; S, 9.04; Br, 22.5. Found: C, 63.3; H, 4.3; S, 9.8; Br, 22.4.

Triphenylmethyl Sulfenyl Iodide.—A suspension of 400 mg of RSCl in 35 ml of petroleum ether is shaken for about 1 min[27] with 550 mg of NaI in 5 ml of acetonitrile. The mixture is washed twice with water, once with 10 ml of 0.05 *N* thiosulfate, and three times with water. After the ethereal layer cools to about −80° a precipitate is obtained which is filtered off at −80°. The precipitate is washed twice with cold petroleum ether and dried with a current of dry air. The apparatus used in the preparation must be rapidly disassembled and the product used up within a few minutes since at room temperature decomposition is complete in about 30 min, yield 40%, deep orange powder. The product can be kept for extended periods under nitrogen in sealed vials at Dry Ice temperature. In the 5–6 min necessary to disassemble the apparatus used in the preparation and to make up a solution, no decomposition occurs (the product is probably still cold). However, as soon as decomposition starts with liberation of iodine, it progresses very rapidly. In solution the product is much more stable even at room temperature, in the absence of light. The presence of iodine catalyzes the decomposition.

Anal. Calcd for $C_{19}H_{15}SI$: S, 7.97; I, 31.55. Found: S, 8.58; I, 30.[28]

The decomposed product consists mostly of iodine, sulfur, and trityl sulfide with a trace of disulfide[29] even though mechanistic analysis of the decomposition[29] shows that the products initially formed are probably iodine and disulfide.

Anal. (of a decomposed sample). Calcd for $C_{19}H_{15}SI$: C, 56.7; H, 3.73; S, 7.97; I, 31.55. Found: C, 57.6; H, 3.8; S, 8.45; I, 30.3.[30]

Triphenylmethyl Sulfenyl Thiocyanate.—A suspension of 0.453 g of RSCl and 0.3 g of NaSCN in 25 ml of acetone is stirred for about 30 min. The mixture is filtered and evaporated in a rotary evaporator. An oil is obtained which yields white crystals upon addition of petroleum ether. The product is recrystallized from benzene–petroleum ether: yield after recrystallization, 50%; mp 101–102°.

Anal. Calcd for $C_{20}H_{15}S_2N$: C, 72.03; H, 4.53; S, 19.22; N, 4.20. Found: C, 72.1; H, 4.5; S, 19.1; N, 4.25.

Kinetics.—Kinetic measurements were carried out by the general technique described earlier[7] at the following wavelengths for RSSCN, RSCl, RSBr, and RSI, respectively: 280, 280, 380, and 440 mμ. A single run with RSI (2.9×10^{-2} *M*) was followed by titration with 0.01 *N* iodate of the iodide formed in the reaction and extracted with water from the benzene solution. At such a high concentration of substrate autocatalysis was so strong that the initial rate could not be measured accurately.

While RSCl and RSSCN could be thoroughly purified, RSBr gives only a fair analysis and RSI has a purity of about 96%. However, the concentration of the substrates was never higher than 1/20 of butylamine and thus a small per cent impurity should not change the kinetics. Although the most likely impurities are sulfur, trityl disulfide, and sulfide, which are not likely to affect the kinetics, several runs were followed in the presence of decomposition products.

The decomposition products of RSBr have been obtained from a sample of the product which had been left for about a week at room temperature. The orange crystals yielded a yellow powder.

The decomposition products of RSI were prepared from a sample of the product left at room temperature for about 2 hr. The mixture, by analogy with the preparation of RSI, was dis-

(24) W. E. Savige and A. Fava, *Chem. Commun.*, 417 (1965).

(25) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(26) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1967, p 402.

(27) A check of the rate of reaction in similar experimental conditions but in homogeneous phase shows that the reaction is over in less than 10 sec.

(28) By titration with iodate after reaction with excess butylamine.

(29) Unpublished data by M. Tentori, E. Ciuffarin, and A. Fava.

(30) By titration with thiosulfate.

solved in petroleum ether and freed from iodine by washing once with 0.05 N thiosulfate and twice with water. The solvent was then stripped at room temperature with a rotary evaporator.

Although RSI and to a lesser degree RSBr are thermally unstable, in solution and in the absence of light they can be kept 1 day or more at room temperature without any detectable decomposition. The uv spectrum is a very good probe for decomposition since in each case the spectrum of the decomposed product is quite different from that of the starting material. The stability depends on the concentration. For example, solutions 10^{-2} M of RSI are stable for about 24 hr in the dark before decomposition starts. At the concentrations used in this paper ($1–2 \times 10^{-4}$ M) the solutions are stable 1 week or more and the limited exposure to light in the spectrophotometer is not sufficient to initiate the decomposition. Solutions of RSBr present an even greater stability.

Products.—N-(*n*-Butyl)triphenylmethylsulfenamide is the only product recovered in the reaction of RSI, RSBr, and RSSCN with *n*-butylamine. To about 1 g of RSI, RSBr, and RSSCN in 20 ml of benzene, *n*-butylamine was added (5% excess) while stirring. The mixture was washed three times with 1 N HCl and three times with water and dried over anhydrous sodium sulfate. The solution was filtered and the solvent stripped in a rotary evaporator. In order to remove all traces of benzene, about 10 ml of petroleum ether was added and evaporated as before. The weight of the oil thus obtained was within 95 and 102% of the stoichiometric yield in sulfenamide. Moreover, the ir spectrum of the oil was identical with that of an authentic sample. After recrystallization from petroleum ether[7] yields of pure, crystalline product ranging from 75 to 85% were obtained.

Registry No.—butylamine, 109-73-9; trityl sulfenyl chloride, 24165-03-5; trityl sulfenyl bromide, 24165-04-6; trityl sulfenyl iodide, 24215-85-8; trityl sulfenyl thiocyanate, 24165-05-7.

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The Synthesis of *cis*-Pulegol and Its Allylomerization Products, 3-*p*-Menthen-8-ol and 3-*p*-Menthen-8-yl Ethers

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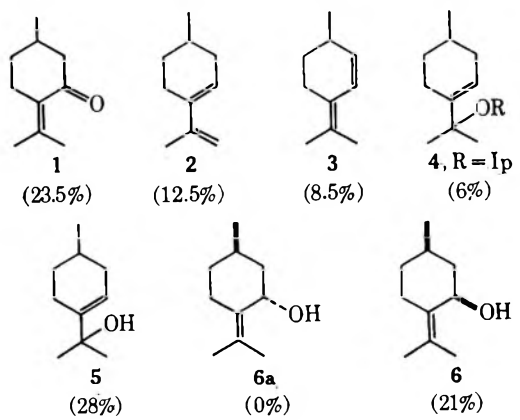
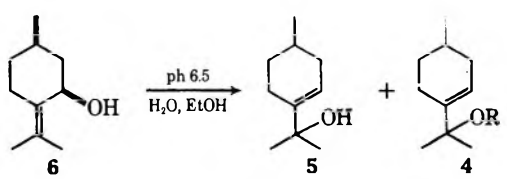
(−)-*cis*-Pulegol (**6**) allylomerizes readily to (+)-3-*p*-menthen-8-ol (**5**), n^{20}D 1.4750, α^{25}D +80°, under mildly acidic conditions. In the presence of alcohols, 3-*p*-menthen-8-yl ethers (**4**) are also formed, while, in the presence of aluminum isopropoxide (AIP), at temperatures above 100°, both **5** and **6** dehydrate, affording a mixture of 3,8-*p*-menthadiene (**2**) and 2,4(8)-*p*-menthadiene (**3**), a fact that may account for the failure of previous workers to isolate pulegols from pulegone (**1**) by a Meerwein–Pondorff–Verley reduction. *trans*-Pulegol (**6a**), because of its greater instability, could not be detected from reduction products of **1** under kinetically or thermally controlled conditions.

In the course of an investigation on the nature of some alcohols related to pulegols, we reviewed the possible synthetic routes for *cis*- and *trans*-pulegol (**6** and **6a**). The AIP reduction of (+)-pulegone (**1**) at 120–170° according to Short and Read[1] yielded, instead of the desired alcohols, mainly 3,8- and 2,4(8) *p*-menthadiene (**2** and **3**) and minute amounts (5%) of an alcohol to which they assigned the structure of neoisopulegol.

Lithium aluminum hydride reduction of (+)-pulegone (**1**) proceeded smoothly and yielded (−)-*cis*-pulegol (**6**), mp 35.5, α^{25}D −80°, in over 99% yield. Similar results were reported by Porsch, *et al.*,[2] with $NaBH_4$. However, in an attempt to synthesize *trans*-pulegol (**6a**) by treating excess triisobutylaluminum (TIBAL) with (+)-pulegone (**1**), under conditions[3] reported to favor kinetically controlled backside attack leading to an axial OH, we obtained none of the expected *trans*-pulegol (**6a**) but, instead, (−)-*cis*-pulegol (**6**), in over 85% yield, together with a small amount (8–10%) of its allylomer, (+)-3-*p*-menthen-8-ol (**5**). When we carried out the reduction of **1**, in isopropyl alcohol (IPA) in the presence of 0.5–1 equiv of AIP at 85° for 4–5 hr, we obtained the following reaction mixture (vpc by order of elution on 20M $^1/_8$-in. column at 200°).



An extension of the reaction time, to complete the conversion of the unreacted pulegone (**1**), resulted only in larger amounts of **2** and **3** being formed. Unreacted pulegone (**1**), which made the separation of 3-*p*-menthen-8-ol (**5**) very difficult, was easily converted into *cis*-pulegol (**6**) by reduction with $LiAlH_4$. If, on the other hand, the unreacted pulegone (**1**) was oximated, with a mixture of $NH_2OH \cdot HCl$, and sodium acetate in aqueous ethanol (pH 6.5), most of the *cis*-pulegol (**6**) was



(1) A. G. Short and J. Read, *J. Chem. Soc.* 1306 (1939); see also Read and Grubb, *ibid.* 242 (1934).

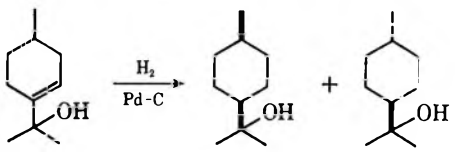
(2) F. Porsch, H. Farnow, and H. Winkler, *Dragoco Rept.*, **4**, 75 (1964).

(3) H. Haubenstock and E. G. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).

allylomerized into 3-*p*-menthen-8-ol (**5**) and 3-*p*-menthen-8-yl ethyl ether (**4**, R = Et). The facile allylomerization of *cis*-pulegol (**6**) to **5** could also be carried out, almost quantitatively, in the presence of 20% acetic acid at 70° with little dehydration to **2** and **3**.

The identity of *cis*-pulegol (**6**) was proven both by hydrogenation, in the presence of Pd–C, to menthol and by its nmr spectrum.

The structure of 3-*p*-menthen-8-ol (**5**) was established by its nmr spectrum and by its hydrogenation with Pd–C into a mixture of 42% *cis*- and 58% *trans*-*p*-menthen-8-ol (**7** and **8**), identical with that obtained



5 **7** (42%) **8** (58%)

from the hydrogenation of α-terpineol under the same conditions. In addition, the presence of a tertiary OH in **5** was proven by running its nmr spectrum in deuterated DMSO which showed a singlet for the hydroxyl proton at δ 4.23.[4]

Experimental Section

Reduction of (+)-Pulegone with AIP (Meerwein–Pondorff–Verley).—(+)-Pulegone (154 g, 1 *M*), $n^{20}D$ 1.4871, $[\alpha]^{25}D$ +23° (purity by vpc 97%+), 350 ml of absolute isopropyl alcohol (IPA), and 35 g of freshly distilled AIP were heated to reflux under a 2-ft Goodloe column while the pot temperature was maintained at 82° and a distillate was collected at 60–64°. After about 4 hr, 60–70 g of acetone–IPA mixture was collected. The excess IPA was then distilled off (pot temperature reaching 90–95°) under partial vacuum and to the cooled (60°) residue of about 160 g was added 300 g of 50% KOH solution and 50 ml of benzene, under agitation, until solution took place. The top layer was separated and distilled in a modified Claisen–Vigreux flask affording a main cut, bp 70–95° (2 mm), 116 g, $n^{20}D$ 1.4840, consisting of 12.5% **2**, 8.5% **3**, 6% **4** (R = Ip), 28% **5**, 23.5% **1**, and 21.5% **6** (vpc 20M 10% column ⅛ in. × 4 m at 150°). The distillate was split in two equal portions and processed as follows.

A. Reduction with $LiAlH_4$.—The distillate (58 g, $n^{20}D$ 1.4840), in 120 ml of dry ether, containing 23.5% unreacted pulegone (**1**) and a total of about 50% alcohols **5** and **6** was fed within 5 min into a solution of 4 g of $LiAlH_4$ in 120 ml of dry ether and heated to reflux for an additional 15 min until the pulegone had completely reacted. The reaction mixture was then decomposed with 10 ml of 50% ethanol followed by 25 ml of water until precipitation of the Al_2O_3. The ether layer was separated and the solvent was evaporated yielding 56 g of crude reaction product consisting of 12.5% **2**, 8.5% **3**, 6% **4** (R = Ip), 29% **5**, and 44% **6**.

B. Oximation with $NH_2OH \cdot HCl$, and Sodium Acetate–Ethanol Solution.— The distillate (58 g), as in A, and 10 g of $NH_2OH \cdot HCl$, 10 g of sodium acetate, 10 ml of water, and 33 ml of ethanol were mixed and agitated at 70° (pH 6.5) for about 2 hr until a sample of the mixture showed the complete disappearance of pulegone (**1**) (by vpc 20M column at 150°). The reaction mixture was washed twice with 100 ml of water and distilled in a modified Claisen–Vigreux flask yielding a main cut, bp 70–100° (2 mm), 45 g, $n^{20}D$ 1.4750, having the following composition (vpc 20M at 140°): 16% **2**, 10.5% **3**, 12.5% **4** (R = Et), 7.5% **4** (R = Ip), 51% **5**, and 2.5% **6**. It was followed by a second cut of pulegone oxime, 13 g, bp 125–135° (2 mm), $n^{20}D$ 1.5050.

Nester–Faust Distillation.—Both reaction products from A and B were distilled through a Nester–Faust Teflon spinning-band column at a reflux ratio of 200:1 and the following pure products were isolated and their structures were confirmed by nmr and ir spectra.

(+)-3-*p*-Menthen-8-ol (5): bp 104° (15 mm); $n^{20}D$ 1.4750; $\alpha^{25}D$ +80°; nmr (Varian A-60A instrument with TMS as internal standard) in deuterated DMSO showed δ 4.24 (s) for a tertiary OH proton,[4] 5.61–5.86 (broad absorption, 1, vinylic), 1.22–2.41 (m, 14, with *gem* dimethyl), 1.31 (s), 0.97 (d, *J* = 5 Hz, CH_3CH); ir 6.91, 7.3, 7.4, 8.2, 8.5, 8.7, 8.9, 9, 9.05, 9.15, 11.2, 11.85, 12.32 μ.

3-*p*-Menthen-8-yl ether (4, R = Et): $n^{20}D$ 1.4588; nmr δ 5.63 (broad, s, 1, vinylic), 3.25 (quadruplet, *J* = 7 Hz, 2, ethoxy methylene), 2.28 (broad m, 7), 1.28 (s, 6, *gem* dimethyl), 1.14 (s of expected t of which 2 outside peaks are masked by other absorption), 0.97 (d, 3, *J* = 7 Hz, CH_3CH); ir 6.9, 7.1, 7.28, 7.32, 7.4, 7.48, 8.05, 8.12, 8.22, 8.37, 8.7, 9.1, 9.4, 9.85, 10.5, 11.12, 11.3, 12.2, 12.35, 12.6 μ.

3-*p*-Menthen-8-yl isopropyl ether (4, R = Ip): nmr δ 3.20–3.75 (broad heptet, 1, of isopropoxy), 5.68 (broad peak, 1, vinylic); ir 6.85, 6.95, 7.25, 7.3, 7.95, 8, 8.12, 8.26, 8.6, 9, 9.1, 9.25, 9.8, 9.95, 10.2, 11, 11.2, 11.7, 12.4, 12.6 μ.

***cis*-Pulegol (6) by $LiAlH_4$ Reduction of *d*-Pulegone (1).**—(+)-Pulegone (80 g), $n^{20}D$ 1.4871, $[\alpha]^{25}D$ +23°, in 160 ml of ether was reduced within 30 min with 7 g of $LiAlH_4$ in 120 ml of ether, under essentially the same conditions described under A. Upon evaporation of the ether and distillation through a modified Claisen–Vigreux flask a main cut, bp 75–76° (2 mm), 72 g, $n^{20}D$ 1.4890, $[\alpha]^{25}D$ −80°, was obtained; the product crystallized and had mp 34–35.5° (99% pure by vpc). The product obtained by Porsch, *et al.*,[2] with $NaBH_4$ had mp 31.5–32.5°; $[\alpha]^{25}D$ −58.4°; nmr δ 5.48–5.60 (broad absorption, 1), 4.36 (broad t, 1, *J* = 6 Hz), 1.35–2.99 (broad m, 7, including OH), 0.86–1.28 (m, 9, with *gem* dimethyl), 0.99–1.10 (*J* = 1 Hz); ir 7.7, 8.85, 9.65, 10.45, 11.05, 11.7 μ.

Reduction of Pulegone (1) with Triisobutylaluminum.—To 48 g of a 50% benzene solution of TIBAL (0.12 mol) (Texas Alkyls) in 60 ml of dry benzene was added, under a nitrogen blanket and within 0.5 hr, 15.2 g (0.1 mol) of pulegone, in 50 ml of dry benzene at 35 ± 5° under agitation. A sample of the reaction product, analyzed by vpc (20M column at 175°), indicated that less than 2% ketone **1** was present. The reaction mixture was decomposed with 30% NaOH and distilled in a Claisen–Vigreux flask yielding 14 g, bp 80–84° (2 mm), $n^{20}D$ 1.4880, consisting of 85% **6**, 1% **1**, 8% **5**, 2% **3**, and 4% **2**.

A. Allylomerization of *cis*-Pulegol (6) to 3-*p*-Menthen-8-ol (5).—*cis*-Pulegol (**6**) (17 g), mp 34–35°, and 85 g of 20% CH_3COOH were heated under agitation for 20–30 min at 70°, until no more *cis*-pulegol (**6**) was present. Upon neutralization with 4% NaOH and distillation in a modified Claisen–Vigreux flask, 16 g, bp 70–75° (2 mm), $n^{20}D$ 1.4760, $\alpha^{25}D$ +72°, was obtained which consisted of 8% **2**, 1% **3**, 88% **5**, and 3% unknown.

B. Allylomerization and Etherification of *cis*-Pulegol (6).

1.—To 10 g of *cis*-pulegol (**6**), 34–35.5°, in 20 g of absolute ethanol was added at room temperature 2 drops of concentrated HCl; after 0.5 hr the reaction mixture consisted of 57% **4** (R = Et) and 43% **5**.

2.—A mixture of 20 g of *cis*-pulegol, 20 g of ethanol, 10 ml of water, and 1 ml of acetic acid was heated for 2 hr at 80°; the reaction mixture consisted of 43% **4** (R = Et), 54% **5**, traces of **2**, and unreacted **6**.

Hydrogenation of *cis*-Pulegol (6).—*cis*-Pulegol (**6**) (10 g), mp 34–35.5°, in 50 ml of ethanol and 1 g of 5% Pd–C catalyst were hydrogenated rapidly (15 min) in a Parr shaker with hydrogen at 50 psi at room temperature and afforded a product (10 g) which crystallized and consisted of 90% methanol, 3% neoisomenthol, and 7% menthone.

Hydrogenation of 3-*p*-Menthen-8-ol (5).—8-*p*-Menthen-8-ol (**5**) (10 g) in 50 ml of ethanol and 1 g of 5% Pd–C catalyst were shaken in a Parr shaker for 1.5 hr with hydrogen at 50 psi at room temperature and afforded 10 g of a product which consisted of 42% **7** and 58% **8** which were identified by ir and vpc comparison with unambiguous samples of **7** and **8** obtained from the hydrogenation of α-terpineol.

Interaction of AIP with *cis*-Pulegol (6) and 3-*p*-Menthen-8-ol (5). **A.**—*cis*-Pulegol (**6**) (5 g), mp 34–35.5°, and 1 g of AIP

(4) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

were heated in a small modified Claisen–Vigreux flask under a slight (20 mm) vacuum while the IPA formed distilled off. The temperature was maintained for 5 min at 130° and the residue was then decomposed with 30% NaOH to yield about 3 g of reaction product consisting of 58% **2**, 39% **3**, and traces of unreacted **6**.

B.—3-*p*-Menthen-8-ol (**5**) (5 g) and 1 g of AIP were treated under the same conditions as described in A and afforded 3 g consisting of 60% **2** and 40% **3**.

Registry No.—**4**, R = Et, 24301-81-3; **4**, R = IP, 24301-82-4; **5**, 24302-23-6; **6**, 22472-80-6.

The Additivity of Mass Spectral Substituent Effects. Cleavage of Benzophenones

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It would be of interest to extend mass spectral steric-effect studies to simple cleavage reactions, but in known examples the observed electronic substituent effect is not great, and it can be expected that the effect of steric inhibition of resonance will not be great either. The theory of mass spectra suggests that multiple substitution may cause a great scattering of points about the correlation line against Hammett σ constants compared with the scatter for singly substituted compounds. This work shows that for doubly substituted benzophenones, the increase in scattering is not so large as to preclude observation of a moderate change in relative intensities owing to steric inhibition of resonance.

The formation of benzoyl ions in the mass spectra of singly substituted benzophenones can be correlated remarkably well with Hammett σ constants.[2] This general type of correlation, in which the relative intensities of benzoyl ion $[A^+]$ with respect to the intensities of the molecular ions $[M^+]$ are plotted against substituent constants as in eq 1, where $Z = [A^+]/[M^+]$, has been found for unsubstituted ions in the spectra of

$$\log (Z/Z_0) = \rho\sigma \qquad (1)$$

other aromatic compounds.[3] An interesting observation made recently is that *ortho*-substituent effects on ion intensities calculated in this fashion may be correlated[4] with *ortho*-substituent constants derived[5] from rates of gas-phase ester pyrolyses; the good correlation supports the validity of the interpretation of the pyrolysis data.

The relationship of eq 1 does not follow[6] from the quasiequilibrium theory of mass spectra,[7] and other explanations have been suggested. It is generally recognized that the equation of relative "rates" of mass spectral processes with intensity ratios is a simplification, and that other factors, notably appearance potentials of fragment ions[8] and the energy distribution of the molecular ions,[9] in principle govern the intensities of peaks in such a fashion that a Hammett plot may be extracted from them. These factors have been summarized.[10-12] Recently attempts have been made to work backward from the existence of correlations with σ constants in mass spectra, specifically correlations of ion intensities, ionization potentials, and appearance potentials of fragments, to derive the form which the energy distribution of molecular ions must have to meet the requirement of an exact fit of the ion intensity data to eq 1.[13] The restrictions imposed for mathematical tractability make this solution of mostly theoretical interest, but the calculation shows that reasonable distributions produced from consideration of the physical processes occurring in electron impact and the energy distribution in the original molecule[14] are fairly similar in form to this distribution, and allows the hope that further refinement of the model employed will give a better understanding of the importance of the energy distribution.

One would anticipate, on the basis of the good correlation of *meta*- and *para*-substituent constants with relative intensities in benzophenone spectra[2] and on the basis that the correlation can be extended remarkably well to *ortho* substituents,[4] that a good correlation could be routinely expected. The present considerations of substituent effects on ion intensities, irrespective of their author, would all predict this in the first approximation, for substituent effects would be expected to be cumulative on electron density, affecting ionization potentials and bond energies in closely similar patterns. It is more important to consider why substituent effects may *not* be cumulative in ion intensity data. The major reason would be the fact that the introduction of more substituents into the aromatic ring affords more routes for decomposition, which will then compete more effectively with formation of the ion of interest, benzoyl. Fewer ions will then decompose by the desired route, and the degree of correlation will be reduced. Further, the introduction of additional complex substituents could alter the effective number of degrees of freedom in the molecular ion to the extent that ion intensities will be noticeably affected. In practice, this alteration has been observed for metastable

(1) Research Fellow of the Alfred P. Sloan Foundation, 1969–1971.
(2) M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 529 (1966).
(3) For a review, see M. M. Bursey, *Org. Mass Spectrom.*, **1**, 31 (1968).
(4) K. K. Lum and G. G. Smith, *J. Org. Chem.*, **34**, 2095 (1969).
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(6) M. S. Chin and A. G. Harrison, *Org. Mass Spectrom.*, **2**, 1073 (1969). We thank Professor Harrison for a copy of this manuscript before publication.
(7) H. M. Rosenstock, M. B. Wallenstein, A. L. Wahrhaftig, and H. Eyring, *Proc. Nat. Acad. Sci. U. S.*, **38**, 667 (1952).
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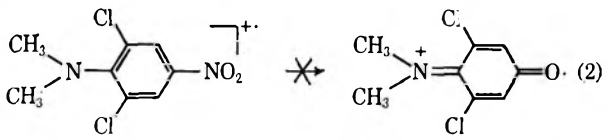
(9) R. S. Ward, R. G. Cooks, and D. H. Williams, *ibid.*, **91**, 2727 (1969).
(10) F. W. McLafferty, *Chem. Commun.*, 956 (1968).
(11) R. G. Cooks, I. Howe, and D. H. Williams, *Org. Mass Spectrom.*, **2**, 137 (1969).
(12) M. M. Bursey and M. K. Hoffman, "Mass Spectrometry, 1970," G. W. A. Milne, Ed., John Wiley & Sons, Inc., New York, N. Y., in press.
(13) R. P. Buck and M. M. Bursey, *Org. Mass Spectrom.*, **3**, 387 (1970).
(14) M. L. Vestal, *J. Chem. Phys.*, **43**, 1356 (1965).

decompositions of the benzoyl ion to $C_6H_5^+$,[15] but it is not significant for the normal benzoyl ions.

Recently, attempts to define effects due to steric inhibition of resonance in mass spectral decompositions have been made.[16-18] In the first examples studied, the stability of the product ion very obviously depended on the ability of an electron donor in the *para* position to interact with the reaction site (eq 2).[16,17] When the group in the *para* position is large, substituents *ortho* to it seem to have the expected effect: there is a very great reduction, by a factor of more than


(2)

20, in the relative intensity of the daughter ion when the group is dimethylamino, which is so large that it is twisted in the ground state, and presumably then cannot interact with the oxygen atom to form a quinonoid structure in the daughter ion.

It is empirically found that the stability of the product ion is a very important "driving force" in governing the intensities of mass spectral peaks.[19-20] It is of interest, therefore, to look at cases where stability of the product ion is not so greatly influenced by the substituent, in order to determine the magnitude of steric effects in cases where the resonance demand is weak; one would expect that, for example, the removal of direct resonance interaction of the substituent and reaction site might reduce the substituent effect to something approaching the field- or induction-effect-dominated *meta*-substituent characteristics, but, before this experiment can be done, it is necessary to establish whether, superimposed upon this presumed steric effect, there will also be a scattering introduced by the increased number of substituents discussed earlier, and, if there is an increase in scattering, whether it will be so great as to imperil the extraction of information about interactions of multiple substituents.

We chose to examine the characteristics of intensity pattterns for the best correlated reaction for single substituents in mass spectra, eq 3, in a very similar

$$YC_6H_4COC_6H_5\cdot^+ \longrightarrow C_6H_5CO^+ \quad (3)$$

$$Y_2C_6H_3COC_6H_5\cdot^+ \longrightarrow C_6H_5CO^+ \quad (4)$$

study for doubly substituted compounds, eq 4. Since the data are highly correlated with σ (or σ^+) values for a single substituent, it seemed acceptable to assume that the correlation of the sum of their σ values (or σ^+ values) with ion intensities would be a measure of the additivity of substituent effects. It is, of course, necessary that one use only substituents which are incapable of exerting an effect other than electrical on neighboring substituents if one wishes to use 3,4-disubstituted compounds. We therefore chose substituents that are cylindrically symmetrical or nearly so to avoid steric effects, or else, as in the case of the nitro group, substituents whose effect is primarily not a resonance effect, as comparison[21] of the *meta* and *para* σ constants seems to suggest.

The point of our experiment, then, was to set up a model to test the additivity of substituent effects on ion intensities in mass spectra. This would determine whether the anticipated scattering of data for the formation of benzoyl ion by competing reactions would be so great that it would prevent the extension of model reactions for the study of steric inhibition of resonance to systems in which the resonance demand of the product ion is low.

Experimental Section

Preparation of Benzophenones.—The compounds were either commercially available or synthesized according to standard procedures in the literature which were checked where advisable to avoid ambiguity in the orientation of products formed by Friedel–Crafts reactions. The compounds were homogeneous by thin layer chromatography and had melting points in agreement with the values reported in the literature.

Mass Spectra.—All the mass spectra were recorded on a Hitachi RMU-6E single-focusing instrument, using 75-eV electrons (emission current 80 μA). The source pressure was always in the range of 5–10 $\times$ 10^{-7} Torr; the source temperature was maintained at 185 $\pm$ 5°. Samples were introduced through the liquid–solid sample introduction port into a reservoir held at 185 $\pm$ 5°. The reproducibility of peak heights was at least 3% for four replicate determinations, and in many cases was less than 1%. Ratios of fragment ion intensities to molecular ion intensities were reproducible from day to day to within 4–5%.

Results and Discussion

Our data are presented in Table I, in the form of simple intensity ratios. When these data are plotted against the sum of the σ constants for each substituent, the correlation illustrated in Figure 1 is obtained. The slope of the correlation line is 0.77; the correlation coefficient is 0.918. When the data are plotted against the sum of the σ^+ constants for each substituent, the correlation shown in Figure 2 is found. Here the slope of the correlation line is 0.55 and the correlation coefficient is 0.956.[22]

TABLE I
RELATIVE INTENSITIES OF m/e 105 IN THE MASS SPECTRA OF DOUBLY SUBSTITUTED BENZOPHENONES (Z = [105$^+$]/[M$\cdot^+$])[a]

Substituents	Z	Substituents	Z
3-CH_3O, 4-CH_3O	−0.48	3-Br, 4-OH	+0.05
3-Br, 4-NH_2	−0.47	H	+0.08
3-CH_3, 4-CH_3O	−0.42	3-Cl, 4-Cl	+0.41
3-CH_3, 4-OH	−0.28	3-Br, 4-Br	+0.42
3-Cl, 4-CH_3O	−0.14	3-Cl, 5-Cl	+0.52
3-Br, 4-CH_3O	−0.10	3-NO_2, 4-Cl	+0.54
3-CH_3, 4-CH_3	0.00	3-Br, 5-Br	+0.63
3-Cl, 4-OH	+0.01		

[a] The ratio found for benzophenone was divided by a statistical factor of 2.

For singly substituted benzophenones, the slope against σ is 1.01 and the correlation coefficient is 0.976; against σ^+, the slope is 0.66 and the correlation coeffi-

(15) M. L. Gross and F. W. McLafferty, *Chem. Commun.*, 254 (1968).
(16) M. M. Bursey, *J. Amer. Chem. Soc.*, **91**, 1861 (1969).
(17) M. M. Bursey and M. K. Hoffman, *ibid.*, **91**, 5023 (1969).
(18) M. M. Bursey, *Org. Mass Spectrom.*, **2**, 907 (1969).
(19) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, p 81.
(20) F. W. McLafferty and M. M. Bursey, *J. Amer. Chem. Soc.*, **90**, 5299 (1968).
(21) R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960).
(22) The values for σ and σ^+ were taken from the tabulation of C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

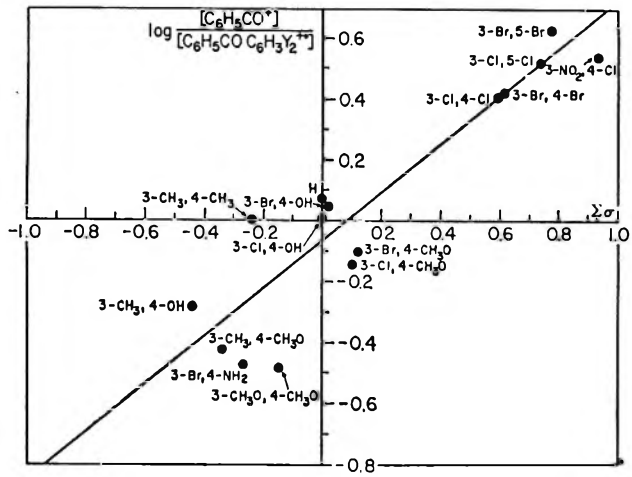


Figure 1.—Correlation of intensity ratios in doubly substituted benzophenones with sums of individual σ values of substituents.[22]

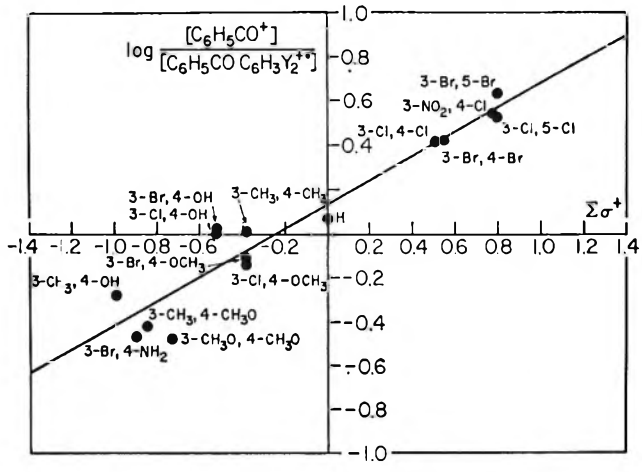


Figure 2.—Correlation of intensity ratios in doubly substituted benzophenones with sums of individual σ^+ values of substituents.[22]

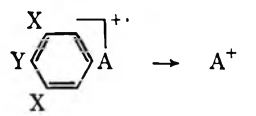
cient is 0.963.[2] These values were determined for more substituents than are represented in Table I, including several whose intensity ratios deviate markedly from the correlation line for explicable reasons. If we consider the correlation of only those single substituents that were actually used in the double-substituent study, their correlation with σ is better: $r = 0.990$. The correlation of data for this limited number of substituents with σ^+ is also improved: $r = 0.982$.

In terms of standard deviations of data points from the correlation line, the standard deviation of the new data from the line against σ is 0.15 log unit, compared with 0.09 for the old data (0.06 for those members of the old data actually used). The standard deviation of the new data from the line against σ^+ is 0.06 log unit, compared with 0.11 for the old data (0.07 for those members of the old data actually used).

As measured by the correlation coefficient, then, the doubly substituted benzophenones do show a decreased correlation with both σ and σ^+ constants, when compared with the data for the singly substituted benzophenones. The correlation against σ^+ is superior for the doubly substituted benzophenones, a distinction that was not noted for the singly substituted benzophenones first studied[2] but noted later when the reaction was examined for the *ortho*-substituted compounds.[4] As measured by the standard deviation of the data points from the correlation line, the correlation with σ^+ is still the better one for the doubly substituted compounds. There is, in fact, a slight decrease in the standard deviation from that of the data points of the single substituents used, but it may not be meaningful.

The data therefore indicate that, first of all, a recognizable correlation still exists for data from doubly substituted benzophenones. The slope of the line is somewhat different from that for the monosubstituted benzophenones, but this could be explained in light of the scattering of the data. The second obvious point is that for the correlation against σ, the scattering is markedly increased, as both the decreased correlation coefficient and simple inspection suggest. The loss in correlation is not so great, however, that much information would be lost about *expected* deviations from the line in other systems because of substituent–substituent interactions, provided that the *expected* deviations from additivity were large enough. For the correlation against σ^+, the loss in correlation is in fact insignificant.

It should be possible, as a result, to uncover deviations from additivity as a result of steric inhibition of resonance or other substituent–substituent interactions. The scattering due to the multiple substitution of systems suggested by eq 5 will increase the probable



(5)

deviation of the intensity ratio, in the benzophenones by a predictable amount, and we can therefore state how large the steric effect on intensity ratios must be in order to assign the deviation from additivity with confidence to the predicted effect, not to the scattering because of multiple pathways.

For the benzophenones, the standard deviation of relative intensity values from the expected values (the correlation line) is 0.06 for the σ^+ correlation. Twice the standard deviation sets the 95% confidence level; that is, outside of this range there is only a 5% chance that any observed effect is due entirely to scattering. Provided that we can find examples where the expected change in substituent effect is greater than 0.12 log unit as a result of steric inhibition of resonance, we can assign deviations from additivity in the proper direction to this cause with a high level of confidence that this is indeed the source of the deviation. If one chooses the worse correlation, that with σ values, then the substituent effect must be greater than 0.30 log unit to ascribe the same level of confidence to the interpretation.

The deviation seems sufficiently small that we have anticipation of finding large enough expected changes in substituent behavior for eq 5 as a result of steric inhibition of resonance in such reactions. We plan to report our results of this new study later.

Acknowledgment.—This study was supported in part by the University Research Council of the University of North Carolina. Jane Rogers and Dean Wilson assisted with syntheses.

Heterocyclic Studies. 31. The Preparation of 3-Diazoacetylpyrazolines and Conversion to Diazabicyclo[3.2.0]heptenones and 1,2-Diazepinones[1]

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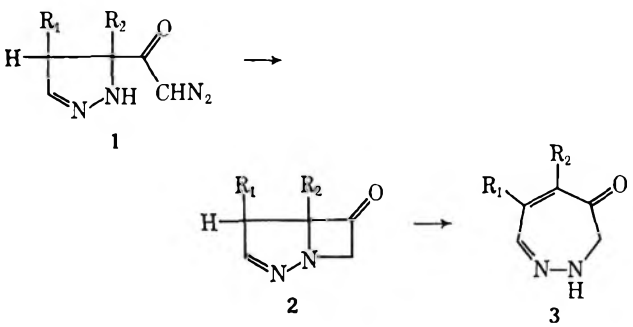
Received December 4, 1969

Diazoacetylpyrazolines **5**, **7**, **13**, and **15** were obtained from the corresponding isomeric α-substituted cinnamic acids. α,β-Unsaturated carboxylic-carbonic anhydrides were found superior to the acid chlorides in the preparation of these 3-diazoacetylpyrazolines. Cyclization of the 3-bromo- (**5** and **7**) and 3-ethoxycarbonyl- (**13** and **15**) pyrazolines to bicyclo[3.2.0]heptenones could not be effected. The 3-bromopyrazoline **5** with base gave 3-diazoacetyl-4-phenylpyrazole. The isomeric 3-diazoacetyl-3,4-diphenyl-1-pyrazolines **16** and **18** were converted to the 5-pyrazolines with base and thence to 1,2-diazabicyclo[3.2.0]heptenones **20** and **21**. Isomerization of **20** and **21** in acetic acid gave the diazepinone **23**. A major side reaction in the base-catalyzed isomerization of **20** and **21** was cleavage to the pyrazoline-N-acetic acids **25** and **26**. Methoxycarbonylpyrazoline (**29**) was prepared from mesaconic acid α-methyl ester and converted to diazepinone **31**.

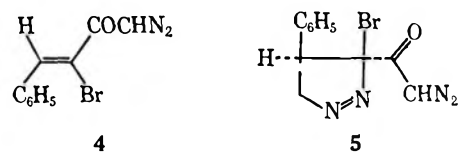
Cyclization of 3-alkyl-3-diazoacetylpyrazolines (**1**) provides an efficient and simple route to the 1,2-diazabicyclo[3.2.0]heptanone (**2**) and 1,2-diazepinone (**3**)



systems.[2,3] The utility of this reaction has led us to prepare some additional pyrazolines and examine the generality of this cyclization and subsequent isomerization to 1,2-diazepines, in particular with respect to the effect of additional functional groups and the configuration of the C-4 substituent in **2**.

The formation of 3-diazoacetylpyrazolines by reaction of α,β-unsaturated acid derivatives with excess diazomethane is potentially a very general method, but for the purpose of this work, there are some restrictions. For the cyclization step, an additional 3 substituent in the pyrazoline ($R_2 \neq H$ in **1**) is required to prevent tautomerization of the initially formed 1-pyrazoline to the 2 isomer. A practical consideration is the necessity of obtaining these rather sensitive diazo ketones in crystalline form to permit isolation; a few attempts to carry reactions through to the bicyclic ketone or diazepine without purification have been unsuccessful. In view of these points, several isomeric pairs of α-substituted cinnamic acids were selected as starting materials.

The first compounds examined were derived from the isomeric α-bromocinnamic acids. The unsaturated diazo ketone **4** and the pyrazoline **5** were readily obtained by reaction of the acid chloride of the (*Z*) isomer[4] ("α-bromo-*trans*-cinnamic acid") with 2 mol of and with excess diazomethane, respectively. The preparation of the acid chloride of the (*E*) isomer ("α-bromo-*cis*-cinnamic acid") was described recently,[5] but we were unable to repeat this work, and another approach was required.



Acylation of diazomethane has almost always been accomplished with an acid chloride; the use of other reagents such as anhydrides is generally less satisfactory. Tarbell and Price reported yields of 57 and 7% for two diazomethyl ketones prepared by the use of mixed carboxylic-carbonic anhydrides.[6] Comparable results were obtained in our hands with benzoic ethylcarbonic anhydride. By using prolonged reaction time, the yield of diazoacetophenone was increased from 7 to 35%, but further improvement could not be achieved.

Although this procedure appeared marginal, it was applied to (*E*)-α-bromocinnamic acid, and treatment of the mixed anhydride with excess diazomethane gave the diazoacetylpyrazoline **7** directly in 30% yield. Subsequent experience with other α,β-unsaturated carboxylic-carbonic anhydrides as noted below has shown that these derivatives are in fact distinctly superior to the acid chloride in most cases, and we have adopted the mixed anhydride procedure as the standard method for preparing 3-diazoacetylpyrazolines. This method obviates the preparation and isolation of the acid chloride, and provides a convenient two-step procedure from acid to diazoacetylpyrazoline in overall yields at least as high as those based upon acid chloride. Another advantage of the mixed anhydrides, presumably, lies in the fact that a mole of diazomethane is not wasted in neutralizing HCl as it is when acid chlorides are used. This point was not directly observed in the present work since excess diazomethane was employed to ensure completion of the addition step, but it was noted in several cases that gas evolution (CO_2) began only after the reaction stood for some time. The acylation step is not dependent on pyrazoline formation,

(1) Supported by Grant GP-5219 from the National Science Foundation.

(2) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Amer. Chem. Soc.*, **84**, 390 (1962).

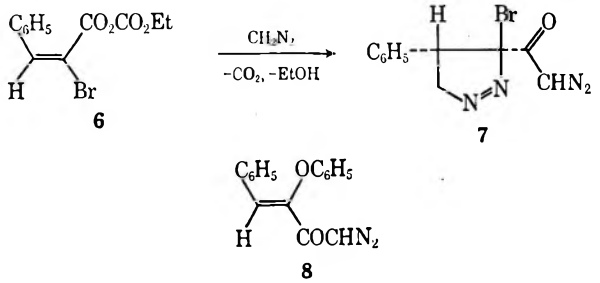
(3) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Winebolt, *J. Org. Chem.*, **31**, 34 (1966).

(4) Notation of J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

(5) A. K. Plisov and I. M. Zhuravleva, *J. Org. Chem. USSR*, **1**, 1893 (1965).

(6) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).

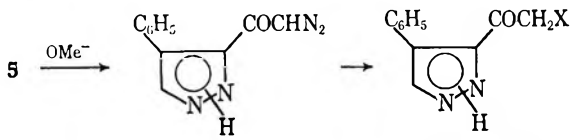
since the mixed anhydride of (*Z*)-α-phenoxycinnamic acid, in which dipolar addition of diazomethane is suppressed, gave the unsaturated diazo ketone **8** in 76% yield.



6 **7** **8**

Cyclization of the pyrazolines **5** and **7** to bicyclic ketones failed. The *cis*-phenylbromopyrazoline **5** was somewhat less reactive toward acid, as judged by nitrogen evolution and disappearance of $COCHN_2$ absorption, than the *cis*-phenylmethyl compound.[2] Under a variety of conditions with acetic, sulfuric, and other acids, any treatment which caused nitrogen evolution invariably gave intractable mixtures. Under forcing conditions, HBr was evolved; a trace of the 3-methoxyacetylpyrazole **10** was obtained from the *trans*-phenylbromopyrazoline **7** in methanolic sulfuric acid.

Treatment of **5** with base gave 3-diazoacetyl-4-phenylpyrazole (**9**) in 75% yield. Two derivatives of this diazo ketone were obtained by standard procedures; no evidence was seen in these reactions of cyclization to a bicyclo[3.2.0] system.

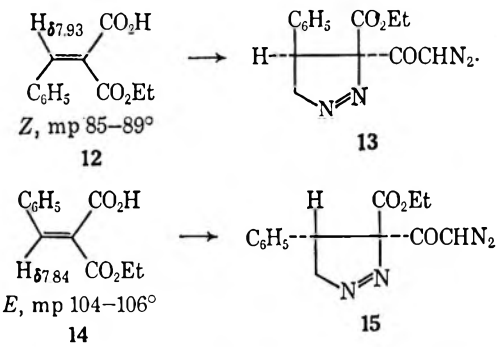


5 **9** **10**, X = OCH_3 **11**, X = Cl

The α-(ethoxycarbonyl)cinnamic acids **12** and **14** provided another potentially interesting pair of isomers for this study. These acids have been described several times,[7,8] but apparently the pure isomers have not been separated. By a modification of the standard barium salt procedure[9] used for the α-bromo acids, an acid [mp 85–89°, δ(–CH=C) 7.93 ppm] was obtained from the less soluble salt, and an isomer [mp 104–106°, δ (–CH=C) 7.84 ppm] was isolated from the soluble salt. The *Z* and *E* configurations **12** and **14** are assigned to these isomers on the basis of the barium salt solubility and vinyl proton chemical shift. In two other pairs of substituted cinnamic acids, α-bromo- and α-phenyl-, the vinyl proton signal appears 0.9–1.0 ppm further downfield in the isomer with β-H and $-CO_2H$ *cis*. A smaller difference is to be expected in the esters **12** and **14** because of the similar shielding effects of the ester and carboxylic acid groups. The difference of 0.09 ppm between **12** and **14** is of questionable significance, but assignment of the *cis*-β-H–CO_2H (*Z*) configuration (**12**) to the acid with the less shielded vinyl proton is also consistent with the lower solubility of the barium salt of this acid. In the α-bromo and α-phenyl series and also unsubstituted cinnamic acids,[10] the less soluble barium salt is that with β-H and CO_2H *cis*.

Diazoacetylpyrazolines **13** and **15** were obtained in high yields by the mixed anhydride procedure. The compounds were isolated without difficulty as solids which decomposed on melting at 50 and 80°, respectively. These diazo ketones are thus relatively stable in comparison with related pyrazolines bearing two electron-accepting groups such as $-CO_2R$ or $-CN$ at C-3; examples of the latter have recently been prepared at −40° and shown to decompose rapidly at temperatures below 0°.[11]

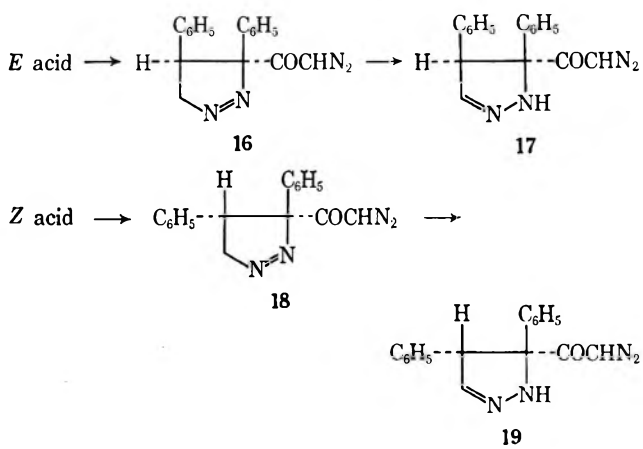
No bicyclic ketones or other products were isolated from the reactions of **13** and **15** with acid, and there was no evidence for four-ring carbonyl absorption in the ir spectra of the crude reaction mixtures. In previous cyclizations to diazabicyclo[3.2.0]heptenones, the 3-alkyl-3-diazoacetyl-1-pyrazolines have been successfully used as the substrate, although it has been shown[2,3] that isomerization to the 5-pyrazoline precedes or accompanies ring closure. The failure of the bromo- and ethoxycarbonylpyrazolines **5**, **7**, **13**, and **15** to undergo cyclization is probably due to the competition of other reactions with the acid-catalyzed tautomerization to the 5-pyrazoline isomers. With the bromo compounds the problem lies in the propensity for elimination leading to pyrazoles. In the case of the esters **13** and **15**, ring opening to a diazonium enolate and loss of nitrogen would be expected to be the major complication.[11]



Z, mp 85–89° **12** **13**

E, mp 104–106° **14** **15**

A pair of stereoisomeric bicyclic ketones was finally obtained in the α-phenylcinnamic acid series. 1-Pyrazolines **16** and **18** were readily prepared from the

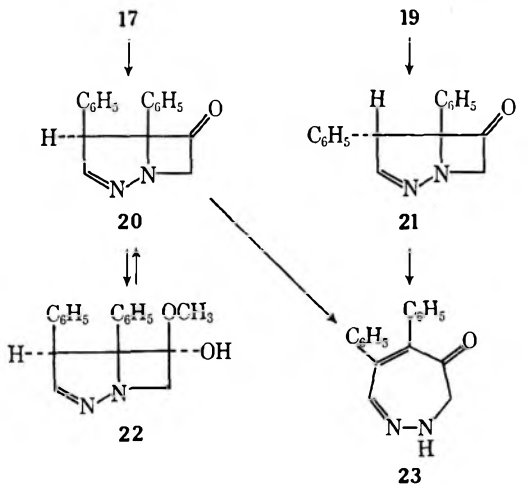


16 **17** **18** **19**

(7) G. Reinicke, *Justus Liebigs Ann. Chem.*, **341**, 89 (1905).
(8) E. J. Corey and G. Frankel, *J. Amer. Chem. Soc.*, **75**, 1168 (1953).
(9) J. J. Sudborough and K. J. Thompson, *J. Chem. Soc.*, **83**, 673 (1903).
(10) S. A. Faseeh, *Pak. J. Sci. Res.*, 63 (1951); *Chem. Abstr.*, **47**, 11159 (1953).
(11) H. Kisch, O. E. Polansky, and P. Schuster, *Tetrahedron Lett.*, 805 (1969).

respective mixed anhydrides, and were converted to the 5-pyrazolines **17** and **19** by treatment with base. These isomerizations required carefully controlled conditions to minimize further reactions which will be described in a later paper.

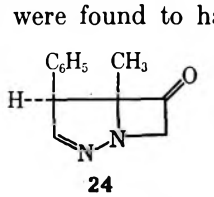
The 5-pyrazolines **17** and **19** were converted to bicyclo[3.2.0] ketones **20** and **21** with cold methanolic sulfuric acid. From the *cis*-diphenylpyrazoline, the hemiketal **22** was obtained as a major by-product; the *exo*-methoxy structure is based on the assumption of



methanol addition at the *exo* side of the carbonyl. Similar rather stable hemiketals were previously observed in the steroidal diazabicyclic ketone series.[2] Compound **22** was extremely labile and reverted rapidly in chloroform solution to the ketone **20**. No ketal was observed in the *trans*-diphenyl series, in which steric interference with the *endo*-phenyl group would be severe.

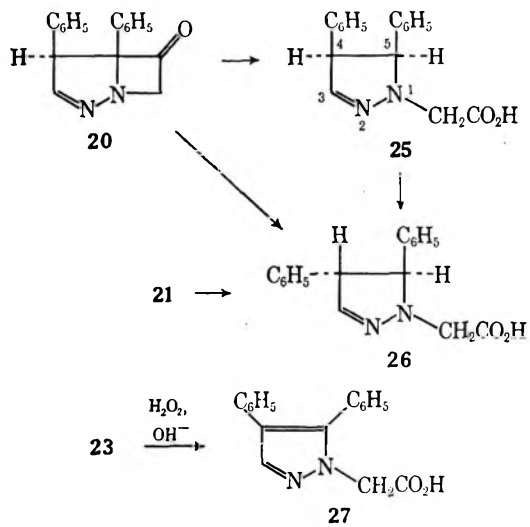
For preparation of the 5,6-diphenyl-2,3-dihydrodiazepinone (**23**), the 1-pyrazoline **16** derived from the less expensive *Z* acid was used. Treatment of **16** with hot acetic acid gave the diazepine in 47% yield. The reaction was not so clean as that in the methylphenyl series,[3] and impurities (by tlc) began to appear before the pyrazoline had completely reacted. The diazepinone **23** had spectral properties very similar to those of the 5-methyl-6-phenyl derivative, with a considerably higher visible absorption maximum (ϵ_{410} 4400 *vs.* 2900).

The yield of **23** from the 1-pyrazoline reflects the combined efficiency of three steps—isomerization to **17**, cyclization to **20**, and ring opening of the bicyclic ketone. The last step has been studied semiquantitatively in the methylphenyl series[3] (compound **24**); in that case the reaction is most effectively catalyzed by base and to a lesser degree by acid. To compare structural and steric effects in this ring-opening step, the rates of conversion of the two diphenylbicyclic ketones **20** and **21** and the *cis*-4-methyl-5-phenyl compound **24** to the respective diazepinones were measured spectrophotometrically in 1 *N* methanolic acetic acid at 35°. The nature of the C-4 substituent and the configuration at C-5 were found to have only a minor influence; the slightly faster rates of **20** and **24** probably reflect somewhat greater eclipsing interactions in the *exo* ketones.



Compd	k_1, l. mol sec^{-1}
20	1.67×10^{-6}
21	0.80×10^{-6}
24	1.38×10^{-6}

Comparison of the rates of the base-catalyzed reactions could not be made because of a major side reaction with the diphenyl ketones. Whereas the reaction of **24** gave a straight-line pseudo-first-order plot to 94% completion in 0.01 *N* methanolic base, the curves for **20** and **21** deviated sharply. The conversion to **23** was 15% with the *exo* isomer (**20**) and 34% with the *endo*-phenyl ketone (**21**). Treatment of **20** with methanolic base gave in low yield an acid which is assigned the *cis*-diphenylpyrazoline acetic acid structure **25**. In the nmr spectrum, H-4 and H-5 had a *cis* coupling of 10.3 Hz, and H-4 was coupled also to H-3 (J = 1.3 Hz); the other peaks were consistent for **25**. In more concentrated aqueous base, both **20** and **21** gave an isomeric acid whose spectrum ($J_{4,5}$ = 13 Hz) indicated the presumably more stable *trans* acid **26**. Surprisingly, attempts to oxidize **25** with MnO_2, $KMnO_4$, or H_2O_2 to the pyrazoleacetic acid **27** were all unsuccessful. A sample of **27** was obtained in very low yield by alkaline peroxide oxidation of the diazepinone **23**.[12]



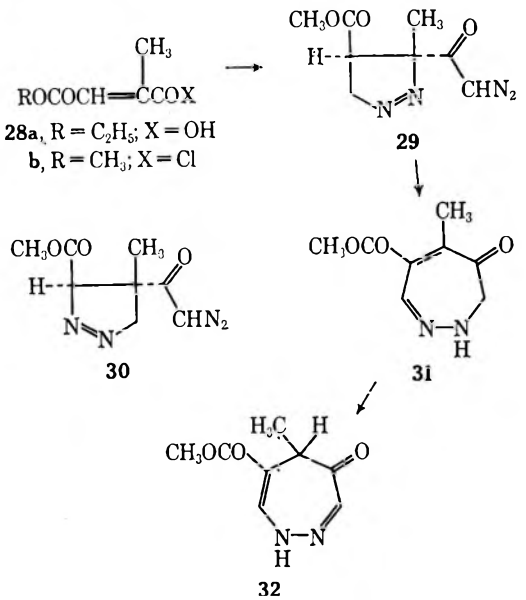
The facile cleavage of ketones **20** and **21**, in contrast to the 4-methyl ketone **24**, is easily understood in view of the stabilization of a carbanion by the phenyl substituent in **20** and **21**. The reaction apparently occurs with fairly complete retention of configuration at C-5, and isomerization of the *cis*-diphenylpyrazoline **25** presumably involves removal of H-4, which is activated by both 4-phenyl and C=N groups. In the 4-methyl ketone **24**, only the H-4 proton is activated toward base, and removal leads to diazepinone formation.

The formation of **23** represents a rather slight extension of the scope of this diazepinone synthesis, and the unsuccessful results with the bromo-, phenoxy-, and ethoxycarbonyl cinnamic acids indicate that α-functional α,β-unsaturated acids cannot be adapted, even in the relatively favorable β-phenyl case, to this sequence. A different approach thus seemed to be required for the synthesis of a functionally substituted diazepinone.

A promising candidate for this purpose was a pyrazoline derived from mesaconic acid "α ester" (**28**, X = OH). The half-esters of mesaconic acid have been known for many years, but some ambiguity has existed regarding the position of the ester function. Cocker

(12) J. A. Moore and C. L. Habraken. *J. Org. Chem.*, **30**, 1889 (1965).

and Fateen have shown conclusively that the monoethyl ester obtained by partial saponification is **28a**.[13] For our purposes the methyl ester was preferred because of the simpler nmr spectrum and the fact that methyl esters are, in general, more readily crystallized than ethyl esters. Assuming by analogy that the monomethyl ester chloride of Anschütz has the structure **28b** as originally formulated,[14] two pyrazolines, **29** and **30**, could arise, depending on the polarization imparted by CO_2Me and $COCHN_2$ groups for cycloaddition. Of these, **30** could not cyclize to a diazabicyclo[3.2.0]-heptenone, but **29** should be a very favorable case, with a stable substituent at C-3 and a highly activated C-4 proton.



Treatment of the acid chloride **28b** with 2 mol of diazomethane gave a very unstable oil from which an unsaturated diazo ketone could not be isolated, but with excess diazomethane, a pyrazoline was obtained in 66% yield. The spectral properties did not distinguish between **29** and **30**, but on reaction with warm acetic acid the diazepinone **31** was produced (45%). The formation of **31** establishes the structure of the pyrazoline as **29**, and, incidentally, provides independent evidence for the correctness of structure **28b** (X = OH) for mesaconic acid α-methyl ester, since neither of the pyrazolines that could be formed from the isomeric "β ester" (**28**, R = H, X = OCH_3) could lead to a diazabicyclic ketone.

The methoxycarbonyldiazepinone **31** was an orange solid, appreciably soluble in water. The spectral properties were consistent with those of **23** and the 5-methyl-6-phenyl derivative. The compound was not stable to storage at room temperature, and no crystalline derivatives have been obtained. Attempted hydrolysis of the ester group with aqueous carbonate followed by neutralization gave an orange solution from which nothing was extracted with chloroform. In DMSO solution containing sodium methoxide, the nmr spectrum of **31** was transformed completely to a spectrum corresponding to that expected for the 1,5-dihydro isomer **32**. The equilibrium **31** $\rightleftarrows$ **32** appears to lie much further to the right than in the corresponding 4-methyl-5-phenyldiazepinones.[15]

In summary, these studies have shown that the formation of 2,3-dihydrodiazepinones by the sequence **1** → **2** → **3** is of some generality, and certain limitations on the possible structural variations have been delineated. The configuration of substituents in the pyrazoline and bicyclic ketone seems to be of little importance in the overall process. It seems reasonable to expect that 5,6-diaryldiazepinones analogous to **23** could be obtained in some variety. A number of transformations of the 5-methyl-6-phenyldiazepinone proceed in preparatively useful fields to give pyridines, pyridazines, pyrroles, and furans with substitution patterns that are rather difficultly accessible by more conventional routes.[16] On the occasion of a need for diaryl counterparts of these compounds, syntheses based on rearrangements of **23** or variants thereof may be quite convenient. The practical difficulties arising from the instability and solubility properties of **31** and, presumably, other nonarylated derivatives would appear to preclude most synthetic applications.

Experimental Section[17]

(*Z*)-α-Bromocinnamoyl chloride,[18] bp 104° (0.5 mm), nmr δ 8.65 (s, 1), was prepared in 92% yield from the *Z* acid and thionyl chloride.

(*Z*)-3-Bromo-1-diazo-4-phenyl-3-buten-2-one (4).—A solution of 3.9 g (16 mmol) of the above acid chloride in 25 ml of ether was added dropwise to a solution of 38 mmol of diazomethane in 120 ml of ether. After standing 2 hr at 0°, the solution was concentrated and a total of 2.0 g (50%) of diazo ketone **4**, mp 69–71°, was obtained in two crops. Recrystallization from ether–pentane gave yellow needles: mp 71–72°; ν_{KBr} 2080 ($COCHN_2$), 1630 cm^{-1} (CO); δ ($CDCl_3$) 6.25 (s, 1), 7.35 (m, 3), 7.8 (m, 2), 8.10 ppm (s, 1).

Anal. Calcd for $C_{10}H_7BrN_2O$: C, 47.84; H, 2.81; N, 11.16. Found: C, 47.58; H, 2.83; N, 10.87.

3*r*-Bromo-3-diazoacetyl-4*c*-phenyl-1-pyrazoline (5).—A solution of 3 g (0.012 mol) of (*Z*)-α-bromocinnamoyl chloride in ether was added to 0.05 mol of diazomethane. After standing at 0° for 2 days, some insoluble material was removed and the solution was evaporated with the temperature not above 0°. Methanol was added to the residue and the solution was chilled in Dry Ice. The yellow solid which separated was collected, washed with cold methanol, and dried to give 1.6 g of pyrazoline **5**, mp ≤5°. Recrystallization from methanol gave pale yellow crystals: mp 46–48°; ν_{KBr} 2090, 1635 cm^{-1}; δ ($CDCl_3$) 3.95 (center line of symmetrical three-line multiplet; X part of ABX), 4.67, 5.00 [eight lines, calculated centers of gravity of AB part of ABX, J_{AB} = |18.2|, J_{AX} = 7.4, J_{BX} = 8.2 Hz], 6.3 (s, 1, CHN_2), 7.3 ppm (s, 5, C_6H_5). Because of the low melting point, the compound could not be dried completely for analysis.

Anal. Calcd for $C_{11}H_9BrN_4O$: C, 45.07; H, 3.09; N, 19.11. Found (dried 24 hr at 25° over P_2O_5): C, 44.47; H, 2.86; N, 18.44.

Treatment of the unsaturated diazo ketone **4** with diazomethane at 0° for 12 hr gave a mixture of equal amounts of **4** and pyrazoline **5** (by nmr analysis); these compounds were not separated by tlc (chloroform–MeOH, 23:2).

Attempted Preparation of (*E*)-α-Bromocinnamoyl Chloride.[5]—A solution of 6.8 g of the *E* acid and 10 g of oxalyl chloride in 10 ml of ether was refluxed for 24 hr. After evaporation, 2 g of the unreacted *E* acid was recovered; distillation at 88° (0.7 mm) [*cf.* ref 5; reaction time 30 min at 50°, distillation at 100–101° (2 mm)] gave 1 g of acid chloride which by nmr was a 1:1 mixture of *E* and *Z* isomers. With thionyl chloride at 40–50°, the acid was recovered unchanged; at 60–70°, crude solids were

(13) W. Cocker and A. K. Fateen, *J. Chem. Soc.*, 2630 (1951).
(14) R. Anschutz, *Justus Liebigs Ann. Chem.*, **353**, 139 (1907).
(15) M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 1369 (1968).
(16) J. A. Moore, *Trans. N. Y. Acad. Sci.*, **27**, 591 (1965).
(17) General procedures are given in paper 22 of this series: J. A. Moore, R. W. Medeiros, and R. L. Williams, *J. Org. Chem.*, **31**, 52 (1966).
(18) H. Staudinger and E. Otto, *Chem. Ber.*, **44**, 1634 (1911).

obtained which gave nmr spectra consistent with the C_6H_5–CHCl–CHBrCO system.

3*r*-Bromo-3-diazoacetyl-4*t*-phenyl-1-pyrazoline (7).—The mixed anhydride (6) of (*E*)-α-bromocinnamic acid[6] was prepared from 2.27 g (0.01 mol) of the *E* acid, 1.08 g of ethyl chloroformate, and 1.03 g of triethylamine in dry ether. After filtration of triethylamine hydrochloride, the ethereal solution was concentrated and was added to an ethereal solution of diazomethane (0.04 mol) at 0°. Gas evolution was observed immediately after addition. The mixture was kept in a refrigerator for 2 days. After removing some precipitate by filtration, the ethereal solution was concentrated under reduced pressure at 0° bath temperature. The yellow crystalline residue was collected, washed with cold methanol, and dried to give 0.9 g (31%) of crude pyrazoline, mp 90° dec. Recrystallization from methanol gave pale yellow crystals: mp 90° dec; ν_{KBr} 2110, 1630 cm^{-1}; δ ($CDCl_3$) 7.4–6.7 (m, 5, aromatic H), 6.22 (s, 1, $COCHN_2$), δ_A 5.17, δ_B 4.78, δ_X 3.90 ppm (J_{AB} = |17.7|, J_{AX} = 6.3, J_{BX} = 1.5 Hz).

Anal. Calcd for $C_{11}H_9BrN_4O$: C, 45.07; H, 3.09; N, 19.11. Found: C, 44.49; H, 2.93; N, 18.45.

(*Z*)-1-Diazo-3-phenoxy-4-phenyl-3-buten-2-one (8).—(*Z*)-α-Phenoxycinnamic acid,[19] mp 180°, 7.2 g (0.03 mol), was converted to the anhydride with 3.25 g of EtOCOCl and 3.1 g of Et_3N as described above, and the filtered ethereal solution of anhydride was added to a solution of 0.08 mol of diazomethane. After the solution had stood at 25° for 1 day and some amorphous solid was removed, the solution was evaporated to give 6.0 g of yellow solid, mp 100°. Recrystallization from methanol gave **8** as yellow crystals: mp 102–103°; ν_{KBr} 2100, 1640, 1580 cm^{-1}; δ ($CDCl_3$) 7.7–6.8 (m, 11, aromatic **H** + vinyl **H**), 5.6 ppm (s, 1, $COCHN_2$).

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.51; H, 4.53; N, 10.46.

No pyrazoline was obtained after further treatment of **8** with 2 equiv of diazomethane for 2 days at 25°.

3-Diazoacetyl-4-phenylpyrazole (9).—To a solution of 1.47 g (0.005 mol) of 3*r*-bromo-3-diazoacetyl-4*c*-phenyl-1-pyrazoline (**5**) in 10 ml of dry methanol was added a solution of 0.36 g (2 equiv) of sodium methoxide in 10 ml of dry methanol at 0°, and the reaction mixture was left standing at 0°. After 30 min, the mixture was poured into ice water and the aqueous solution was neutralized with acetic acid (pH 6). The yellow crystalline material which separated was extracted with methylene chloride and the organic layer was washed with water, dried, and evaporated to give 0.55 g (76%) of crude pyrazole, mp 150° dec. Recrystallization from methanol and water gave fine needles of **9**: mp 153° dec; ν_{KBr} 3050, 2080, 1590 cm^{-1}; δ (DMSO-d_6) 6.5 (s, 1), 7.2–7.8 (m, 5), 8.02 (s, 1), 13.5 ppm (s, 1).

Anal. Calcd for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.09; H, 3.81; N, 26.16.

3-Methoxyacetyl-4-phenylpyrazole (10).—The diazo ketone **9**, 212 mg, was dissolved in 10 ml of methanol and to the solution was added 0.02 ml of concentrated sulfuric acid at 0°. Gas evolution took place immediately. After the solution had stood at 25° for 30 min, white crystals appeared which were collected; concentration of the filtrate gave additional product; the total yield was 210 mg (97%), mp 200°. Recrystallization from methanol gave needles of **10**: mp 205° with preliminary coloration; ν_{KBr} 3000, 1690 cm^{-1}; δ (DMSO-d_6) 8.04 (s, 1, **H**-5), 7.7–7.2 (m, 5, aromatic **H**), 4.74 (s, 2, $COCH_2OCH_3$), 3.4 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.83; H, 5.51; N, 13.02.

3-Chloroacetyl-4-phenylpyrazole (11).—A solution of 424 mg of **9** in 5 ml of tetrahydrofuran mixed with a solution of 400 mg of **12** *N* HCl in 5 ml of THF at 0°. Gas evolution began at 0° and became vigorous as the solution was warmed; after standing at 25° for 30 min, the solution was concentrated *in vacuo*. Addition of water to the residue gave white crystals which were collected on a filter and dried to give 433 mg (96%) of solid, mp 185° (darkening). Recrystallization from methanol gave **11**: mp 185° (darkening); ν_{KBr} 3070, 1690 cm^{-1}; δ (DMSO-d_6) 8.1 (s, 1, **H**-5), 7.6–7.2 (m, 5, aromatic **H**), 5.05 ppm (s, 2, $COCH_2Cl$).

Anal. Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 60.00; H, 3.84; N, 12.55.

(19) Prepared according to "Beilstein's Handbuch," 4th ed, Vol. 10, p 303, lit. mp 179°.

Treatment of **11** with methanolic NaOH overnight at 30° gave the methoxyacetylpyrazole **10**.

Separation of (*E*)- and (*Z*)-α-(Ethoxycarbonyl)cinnamic Acids.—A mixture of (*E*)- and (*Z*)-α-ethoxycarbonylcinnamic acids (benzylidene malonic acid monoethyl esters) was prepared from ethyl potassium malonate, benzaldehyde, and acetic acid.[7] The mixture contained *Z* and *E* acids in a 63:37 ratio (by nmr).

The mixture, 13 g, was suspended in 300 ml of water, and a total of 5 ml of concentrated aqueous NH_4OH was added in small portions until a clear solution was obtained. Solid $BaCl_2$ was added to the solution until saturation. After the solution was stirred for 3 hr, the white precipitate was collected and washed with saturated aqueous $BaCl_2$. This barium salt was decomposed with 2 *N* HCl and the oily acid was extracted with ether. The ethereal solution was washed with water, dried, and evaporated to a colorless residue which crystallized on cooling. It was washed with pentane and dried to give 6 g of the crude *Z* acid (α-ethoxycarbonyl-*trans*-cinnamic acid, **12**): mp *ca.* 85°; δ ($CDCl_3$), 10.8 (s, 1, **COOH**), 7.93 (s, 1, **CH**=C), 7.44 (s, 5), 4.37 (q, *J* = 7 Hz, 2, CH_2), 1.26 (ppm (t, *J* = 7 Hz, 3, CH_3). After several recrystallizations from benzene and pentane, the melting point became 85–89°.

The filtrate from the barium salt of the *Z* acid was acidified and the oily material which separated was extracted with ether. After drying and evaporation, 3 g of solid, mp 80–90°, was obtained. Nmr indicated a mixture of 90% *E* and 10% *Z* acid. After several recrystallizations from benzene and pentane, almost pure *E* acid **14**, mp 104–106°, was obtained: δ ($CDCl_3$) 10.67 (s, 1, **COOH**), 7.84 (s, 1, **CH**=C), 7.4 (m, 5), 4.32 (q, *J* = 7 Hz, 2), 1.32 ppm (t, *J* = 7 Hz, 3).

Ethyl 3-Diazoacetyl-4*c*-phenyl-1-pyrazoline-3*r*-carboxylate (13).—The mixed anhydride of (*Z*)-α-ethoxycarbonylcinnamic acid and ethyl hydrogen carbonate was prepared from 4.4 g (0.02 mol) of the *Z* acid **12**, as described for **6**. After concentrating the ethereal solution, it was added to an ethereal solution of 0.05 mol of diazomethane at 0°. The reaction mixture was allowed to warm to room temperature overnight. After removal of some insoluble material by filtration, the reaction mixture was concentrated *in vacuo* to give a thick yellow oil, which was stored in a Dry Ice box for 5 days. Small amounts of ether and pentane were then added and the oil was rubbed with a spatula. Crystallization occurred and 4.5 g (79%) of crude pyrazoline, mp 48°, was obtained. Recrystallization from ether–pentane gave **13**: mp 50–53° dec; ν_{KBr} 2100, 1740, 1635 cm^{-1}; δ ($CDCl_3$) 7.2 (m, 5, aromatic **H**), 6.05 (s, 1, $COCHN_2$), 5.0–4.1 (m, 3, ring **H**), 3.75 (q, *J* = 7 Hz, 2, CH_2), 0.80 ppm (t, *J* = 7 Hz), 3, CH_3).

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.65; H, 4.96; N, 18.85, 18.82.

Ethyl 3-Diazoacetyl-4*t*-phenyl-1-pyrazoline-3*r*-carboxylate (15).—By the procedure described above, 2.2 g of the *E* acid **14** was converted to the pyrazoline **15**. The crude solid, obtained in 94% yield, was recrystallized from ether: mp 85–87° dec; ν_{KBr} 2110, 1740, 1625 cm^{-1}; δ ($CDCl_3$) 7.4–6.8 (m, 5, aromatic **H**), 5.8 (s, 1, $COCHN_2$), 5.54–4.0 (m, 5, ring H + CH_2CH_3), 1.3 ppm (t, *J* = 7 Hz, 3, CH_3).

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.68; H, 4.94; N, 19.12.

3-Diazoacetyl-3,4-*cis*-diphenyl-1-pyrazoline (16).—The mixed anhydride of (*E*)-α-phenylcinnamic acid [$\delta_{\beta\text{-H}}$ ($CDCl_3$) 8.08 ppm] and ethyl chloroformate was prepared from 2.24 g (0.01 mol) of the acid, 1.09 g (0.01 mol) of ethyl chloroformate, and 1.03 g (0.0102 mol) of triethylamine in dry ether. After removal of Et_3NHCl, the ethereal solution of the mixed anhydride was concentrated and added to an ethereal solution of 0.04 mol of diazomethane. Gas evolution was observed after 2–3 hr. The reaction mixture was left standing at room temperature for one day, filtered, and concentrated to give a yellow oil which was crystallized by addition of methanol and chilling to −50°. The yellow solid was collected, washed with pentane, and dried to give 2.2 g (76%) of crude 1-pyrazoline, mp 60°. Recrystallization from ether–pentane gave pale yellow crystals of **16**: mp 62–64°; ν_{KBr} 2100, 1640 cm^{-1}; δ ($CDCl_3$) 7.2–6.5, (m, 10, aromatic **H**), 5.67 (s, 1, $COCHN_2$), 5.0–4.25 ppm (m, 3, did not fit simple ABX pattern).

Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.25; H, 4.84; N, 18.88.

3-Diazoacetyl-3,4-*trans*-diphenyl-1-pyrazoline (18).—(*Z*)-α-Phenylcinnamic acid, mp 135–138°, $\delta_{\beta\text{-H}}$ ($CDCl_3$) 7.20 ppm, was prepared by photolysis of the *E* isomer and separated by differ-

ential acidification.[20,21] The mixed anhydride was prepared from 22.4 (0.1 mol) of acid and converted to the pyrazoline with 0.4 mol of diazomethane as described for **16**. Pale yellow crystals separated from the dilute ethereal solution after two days. A total of 23.5 g of **18** (81%), mp 150° dec, was obtained (recrystallization from methanol raised the melting point to 157° dec): ν_{KBr} 2100, 1630 cm^{-1}; δ ($CDCl_3$) 7.7–6.9 (m, 10, aromatic **H**), 6.00 (s, 1, $COCHN_2$), 5.3–4.2 (AB part of ABX, δ_A 5.05, δ_B 4.45, J_{AB} = |17.0|, J_{AX} = 7.5, J_{BX} = 2.5 Hz, 2, C-5 CH_2), 3.8–3.6 ppm (X part of ABX, δ_1 3.73, 1, **H**-4).

Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.14; H, 4.73; N, 18.75.

3-Diazoacetyl-3,4-*cis*-diphenyl-5-pyrazoline (17).—To a solution of 5.80 g of 1-pyrazoline **16** in 100 ml of methanol was added 1.0 ml of 1 *N* KOH (in methanol) at 0°. The reaction mixture was left standing at 0° for 4 hr. Dry Ice was then added and the solution was concentrated under reduced pressure to give off-white crystals which were collected and washed with a mixture of ether and pentane. A second crop was obtained from the mother liquor; after recrystallization from ether–pentane, it was combined with the first crop to give a total of 3.85 g (65.5%) of **17**, mp 125–127° dec. The analytical sample was recrystallized from ether and *n*-pentane: mp 125–127° dec; ν_{KBr} 3240, 2100, 1630 cm^{-1}; δ ($CDCl_3$) *ca.* 7 (m, 10, aromatic H), 6.9 (d, J = 1.7 Hz, 1, 5 H), 6.4 (s, 1, NH), 5.33 (s, 1, $COCHN_2$), 5.18 ppm (d, J = 1.7 Hz, 1, 4 H).

Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.18; H, 4.96; N, 19.13.

3-Diazoacetyl-3,4-*trans*-diphenyl-5-pyrazoline (19).—To a solution of 580 mg of the 1-pyrazoline **18** in 10 ml of THF and 10 ml of methanol was added 0.2 ml of 1 *N* KOH. The mixture was left standing at room temperature for 4 hr; tlc showed that some **18** remained and that a second product, slower moving than **22**, was also being formed. After neutralization of the reaction mixture, it was concentrated to give a yellow crystalline residue. Recrystallization from methanol gave 255 mg (44%) of 5-pyrazoline (5% impurity by nmr), mp 130° dec. Recrystallization from methanol gave pure **19**: mp 133° dec; ν_{KBr} 3230, 2100, 1625 cm^{-1}; δ ($CDCl_3$) 7.7–7.0 (m, 10, aromatic H), 6.83 [d, J = 1.5 Hz, 1, H-5], 6.67 (s, 1, NH), 5.33 (s, 1, $COCHN_2$), 4.73 ppm (d, J = 1.5 Hz, 1, H-4).

Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.19; H, 4.83; N, 19.00.

4-*endo*-5-Diphenyl-1,2-diazabicyclo[3.2.0]-2-hepten-6-one (21).—A solution of 1.16 g of the *trans*-Δ^5-pyrazoline **19** in 30 ml of methanol was treated with a solution of 300 mg (1.5 equiv) of concentrated sulfuric acid in 5 ml of methanol at room temperature. After 20 min, the reaction mixture was poured into ice water and the aqueous mixture was neutralized with $NaHCO_2$ and extracted with ether. After washing and drying, the ether was evaporated to give a yellow residue, which was extracted with boiling hexane. Concentration of the hexane solution gave white crystals of **21**: mp 80–81° ((recrystallization from hexane did not change the melting point); ν_{KBr} 1800 cm^{-1}; δ ($CDCl_3$) 7.5–7.0 (m, 11, aromatic H + **H**-3, AB of C-7 CH_2, δ_A 4.70, dd, J_{3-7A} = 1.2 Hz, δ_B 4.42, dd, J_{3-7B} = 1.0 Hz, J_{AB} = |16| Hz), 4.32 ppm (d, J = 1.0, 1, H-4).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.83; H, 5.45; N, 10.78.

4-*exo*-4,5-Diphenyl-1,2-diazabicyclo[3.2.0]-2-hepten-6-one (20) and 6-*exo*-Methoxy-4-*exo*-4,5-diphenyl-1,2-diazabicyclo[3.2.0]-2-hepten-6-*endo*-ol (22).—The 5-pyrazoline **17** (3.85 g, 0.013 mol) was dissolved in 70 ml of methanol and to the solution was added a solution of 1 g (1.5 equiv) of concentrated H_2SO_4 in methanol at room temperature. After the addition, the reaction mixture was stirred at 0° for 10 min and then poured into ice water. After extraction with CH_2Cl_2, the organic layer was washed with dilute $NaHCO_3$ solution and water, dried, and evaporated to dryness. The yellow residue was extracted several times with boiling hexane. The white crystals which remained undissolved were collected and dried to give 730 mg of hemiketal **22**, mp ~125°.

The hexane solution was evaporated to dryness and the residue was slowly recrystallized from hexane to give 2.2 g (65%) of off-white crystals of ketone **20**: mp 108–110°; ν_{KBr} 1790 cm^{-1}; δ ($CDCl_3$) 7.5–6.7 (m, 11, 2 C_6H_5 + **H**-3), 4.86 ppm (d, J = 1.6 Hz, 1, **H**-4, AB of C-7 CH_2, δ_A 4.83, dd, J_{3-7A} = 1.4 Hz, δ_B 4.32, d, J_{AB} = |16| Hz).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.93; H, 5.32; N, 10.68.

The ir spectrum of the hexane-insoluble solid (**22**) contained a very small peak at 1790 cm^{-1} due to **20** and a broad band around 3000 cm^{-1}. This material was dissolved in methanol at room temperature and cooled in a Dry Ice box after addition of a small amount of hexane. The white crystals thus obtained had a very small absorption at 1790 cm^{-1}; mp 125°; δ (DMSO-d_6) ~6.9 (m, 11, 2 C_6H_5 + **H**-3), 5.17 (d, J = 2 Hz, 1, **H**-4, AB of C-7 CH_2, δ_A 3.87, δ_B 3.43, J_{AB} = |11| Hz), 2.97 ppm (s, 3, OCH_3).

The nmr spectrum in DMSO-d_6 gradually changed on standing at room temperature. After 2 days, the presence of **20** and methanol was quite clear and after 4 days, 30% of the methoxy protons were present as methanol. (In $CDCl_3$, this change was complete in a few hours.)

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.78; H, 6.18; N, 9.46.

2,3-Dihydro-5,6-diphenyl-1,2-diazepin-4-one (23).—The Δ^1-pyrazoline **16** (17.4 g, 0.06 mol) was dissolved in 100 ml of acetic acid, and the solution was heated at 90° for 5.5 hr. Tlc showed that some starting material remained at this point and some slower-moving products were being formed. Acetic acid was removed by distillation at reduced pressure. Addition of methanol to the residue gave dark orange crystals which were collected, washed with methanol, and dried to give 6.5 g (47%) of crude **23**, mp 195–198° dec. The diazepinone was recrystallized from ethanol: mp 195–198° dec; ν_{KBr} 3200, 1630 cm^{-1}; δ (DMSO-d_6) ~7.1 (m, 12, 2 C_6H_5, **H**-7 and **NH**), 3.92 ppm (s, 2, CH_2).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.92; H, 5.41; N, 10.59.

2-Acetyl-2,3-dihydro-5,6-diphenyl-1,2-diazepin-4-one was prepared by treatment of **23** with acetic anhydride and pyridine for 3 hr at 26°. After pouring the solution into ice water, the product was collected and recrystallized from chloroform–hexane as light orange crystals: mp 158–160°; ν_{KBr} 1700, 1670 cm^{-1}; δ ($CDCl_3$) 7.48 (s, 1, **H**-7), 7.15 (m, 10), 4.8 (s, 2), 2.45 ppm (s, 3).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.89; H, 5.35; N, 8.95.

Isomerization Rates of Bicyclic Ketones.—Samples of the ketones **20**, **21**, and **24** (0.05 mmol) were accurately weighed and added (t = 0) to 25.0 ml of 1 *N* methanolic acetic acid which had been standing in a bath at 35 ± 0.5°. At appropriate intervals (30, 60, 120 min), the absorbance of the solution at the long-wavelength maximum of the diazepinone (410 mμ for **23**; 401 mμ for the 5-methyldiazepine) was measured on a Cary 14 spectrophotometer. Plots of log $A_\infty/(A_\infty - A)$ *vs.* time gave straight lines; values of k were obtained by a least-squares calculations.

***cis*-4,5-Diphenyl-2-pyrazoline-1-acetic Acid (25).**—A solution of 380 mg of the 4-*exo*-diphenyl bicyclic ketone **20** in 10 ml of methanol was treated with 3 ml of 1 *N* methanolic KOH. On standing at 25° the solution became yellow; after 2 hr, ice water was added and the mixture was extracted with CH_2Cl_2 to remove **23**. The colorless aqueous solution was acifiied and extracted with ether. After washing and drying, the ether layer was evaporated to a crystalline residue. Recrystallization from ether–pentane gave 70 mg (17%) of the *cis*-pyrazoline **25**: mp 150–153° dec (recrystallization from chloroform–pentane gave crystals with the same melting point); ν_{KBr} 1730 cm^{-1}; δ ($CDCl_3$) 9.48 (s, 1, CO_2H), 7.4–6.7 (m, 11, 2 C_6H_5 + **H**-3), 4.87 (d, J_{4-5} = 10.3 Hz, 1, **H**-5), 4.33 ppm (dd, J_{4-5} = 10.3 Hz, J_{3-4} = 1.5 Hz, 1, **H**-4, AB of CH_2CO_2H, δ_A 4.10, d, δ_B 3.62, d, J_{AB} = |17| Hz).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.74; N, 9.99. Found: C, 72.52; H, 5.78; N, 9.86.

***trans*-4,5-Diphenyl-2-pyrazoline-1-acetic Acid (26).**—Compound **20** (200 mg) was added to 5 ml of 30% aqueous KOH solution. The solid dissolved and then some insoluble solid separated which redissolved on addition of water. After 4 hr the colorless solution was neutralized with HCl and extracted with CH_2Cl_2. Evaporation of the dried organic layer gave 140 mg (66%) of white crystalline solid, mp 153–155°. Recrystallization from ether gave pure **26**: mp 153–155°; δ ($CDCl_3$) 11.2 (s, 1, CO_2H), 7.3 (s, 10, 2 C_6H_5), 6.8 (s, 1, **H**-3), 4.48 (d, $J_{4,5}$ = 13 Hz, 1, **H**-5), 4.15 (d, $J_{4,5}$ = 13 Hz, 1, **H**-4), 4.06, 3.65 ppm (AB, J = |17| Hz, 2, $-CH_2-$).

(20) R. Stoermer and G. Voht, *Justus Liebigs Ann. Chem.*, **409**, 36 (1915), report mp 137–138°.

(21) Samples of comparable purity were also obtained from Frinton Chemical Co.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.74; N, 9.99. Found: C, 73.15; H, 5.76; N, 9.88.

A mixture of **25** and **26** was dissolved in 30% aqueous KOH for 1 hr. After isolation, the nmr showed the presence of only **26**.

Reaction of 4-*endo*-phenyl ketone **21** in aqueous base gave **26**, mp 153–155°, ir and nmr identical with those of **26** prepared from **20**.

4,5-Diphenylpyrazole-1-acetic Acid (27).—To a solution of 520 mg of diazepinone **23** in 20 ml of methanol was added 4 ml of 30% hydrogen peroxide; part of the starting material precipitated. After stirring for 2 days, the reaction mixture was added to water and the suspension was extracted with chloroform. The aqueous layer was treated with 2 *N* HCl until turbid and extracted with chloroform. The chloroform layers were washed, dried, and evaporated to a syrup. Addition of ether and pentane caused white solid, mp 70–160°, to separate. Recrystallization from chloroform–pentane gave 40 mg of **27** (7%): mp 170–171°; ν_{KBr} 1725 cm^{-1}; δ ($CDCl_3$) 12.5 (s, 1, CO_2H), 7.87 (s, 1, H-3), 7.5–7.1 (m, 10, 2 C_6H_5), 4.75 ppm (s, 2, CH_2CO_2H).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.38; H, 5.01; N, 10.04.

Methyl 3-Diazoacetyl-3*c*-methyl-1-pyrazoline-4*r*-carboxylate (29).—A solution of 26 g (0.16 mol) of acid chloride **28b**,[14] bp 66–68° (5 mm), in 120 ml of ether was added to a solution of 0.75 mol of diazomethane in ether. After standing at 0° for 4 days, the yellow solution was filtered and concentrated at reduced pressure to an oil. Addition of a few milliliters of ethanol and scratching caused crystallization; a total of 22 g of lemon yellow crystals of **29**, mp 73–74°, was obtained in several crops. Recrystallization from ethanol gave crystals: mp 75–76°; ν_{KBr} 2070, 1710, 1620; δ ($CDCl_3$) 5.82 (s, 1, CHN_2), 4.91–3.2 (m, 3, apparent ABC pattern of H-4 and H-5), 3.71 (s, 3, OCH_3), 1.50 ppm (s, 3, CH_3).

Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.80; H, 4.71; N, 26.45.

6-Methoxycarbonyl-5-methyl-2,3-dihydro-4H-1,2-diazepin-4-one (31).—A solution of 20 g of pyrazoline **29** in 100 ml of acetic acid was warmed at 75–80° for 4.5 hr; tlc showed that some starting material remained and that additional products were beginning to accumulate at this point. The solution was evaporated *in vacuo*, and reevaporated after addition of benzene until the acetic acid odor had disappeared. The red syrup was seeded with crystalline sample obtained from chromatography of a previous preparation; 2.1 g of thick orange prisms of **31**, mp 92–96°, was obtained. The remaining material was absorbed on a column of silicic acid and eluted with chloroform to give an additional 5.8 g of **31** (total 45%) and 2.6 g of unreacted **29**. Recrystallization of **31** from ether gave bright orange prisms: mp 95–96°; ν_{KBr} 3300, 1730, 1640 cm^{-1}; λ_{max}^{MeOH} 222 (ϵ 9700), 260 (infl 3100), 322 (3000), 406 mμ (2450); δ ($CDCl_3$) 7–7.4 (br, 1, NH), 3.93 (s, 3, OCH_3), 3.78 (m, 2, $-CH_2-$, → singlet in D_2O), 2.12 ppm (s, 3, 5-CH_3).

Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.40; H, 5.56; N, 15.08.

On standing, the diazepine darkened and became gummy; such samples were most easily purified by sublimation.

For conversion to the 1,5-dihydro isomer **32** a solution of 91 mg (0.5 mmol) of **31** in 2 ml of dimethyl sulfoxide was treated with 0.05 mequiv of sodium methoxide (0.02 ml of 2.6 *N* in methanol). One portion of this solution was stored at 30° and the other at 62°. After 67 hr, the nmr spectrum of the 30° solution showed 65 ± 10% of the 1,5 isomer [doublets due to H-3 and H-7 at 7.36 and 7.66 ppm *vs.* DMSO (δ 2.62), singlet due to H-7 in the 2,3-dihydro isomer at 7.01 ppm]. The spectrum of the 62° solution showed no peak at 7.01 ppm.

The 30° solution was then warmed to 2 days at 60° and the combined DMSO solutions were poured into 25 ml of water. The mixture was extracted with CH_2Cl_2 and the extract was washed, dried, and evaporated to 80 mg of dark oil. Chromatography on silicic acid gave a yellow oil which did not crystallize: δ ($CDCl_3$) 7.7 (d, $J \sim 1$ Hz, 1), 7.60 (d, $J - 1$ Hz, 1), 4.0 (m, 1, H-5), 3.8 (s, 3, OCH_3), 1.0 ppm (d, $J = 7.5$ Hz, 3).

Registry No.—**4**, 24302-26-9; **5**, 24302-27-0; **7**, 24302-28-1; **8**, 24302-09-8; **9**, 24301-62-0; **10**, 24301-63-1; **11**, 24301-64-2; **12**, 24302-10-1; **13**, 24302-11-2; **14**, 24302-12-3; **15**, 24302-13-4; **16**, 24302-14-5; **17**, 24302-15-6; **18**, 24302-16-7; **19**, 24302-17-8; **20**, 24302-18-9; **21**, 24302-19-0; **22**, 24301-65-3; **23**, 24301-66-4; **25**, 24302-20-3; **26**, 24302-21-4; **27**, 24301-67-5; **29**, 24302-22-5; **31**, 24301-68-6; 2-acetyl-2,3-dihydro-5,6-diphenyl-1,2-diazepin-4-one, 24301-69-7.

Heterocyclic Studies. 32. Some Reactions of 3-Diazoacetyl-4-phenylpyrazoline. A Correction on 1-Diazoacetyl-4-phenyl-3-buten-2-one[1]

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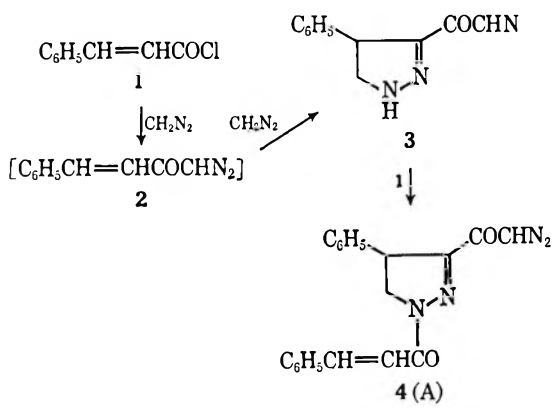
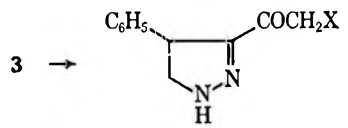
In the course of work on the cyclization of diazoacetylpyrazolines, the unsaturated diazo ketone **2** was of interest as a possible source of 5(3)-diazoacetyl-3(5)-pyrazolinecarboxylic ester, which would arise by addition of diazoacetic ester. The preparation of **2**, mp 172°, has been reported by the reaction of *trans*-cinnamoyl chloride and a limited amount of diazomethane at low temperature.[2] The diazoacetylpyrazoline **3** or the unstable Δ^1 isomer are obtained under the usual conditions with excess diazomethane.[2,3]

We have repeated the procedure for the preparation of the diazo ketone **2** and isolated a product (A) with melting point and ir spectrum corresponding to those reported.[2] However, the nmr spectrum immediately ruled out the proposed structure **2**, and the chloro ketone derived from A differed widely in melting point from that reported for 1-chloro-4-phenyl-3-buten-2-one.[4] The nmr spectra of A and the chloro ketone were also inconsistent with the 5-cinnamoylpyrazoline which might arise by addition of the diazomethyl group of one molecule of **2** to the unsaturated carbonyl group of another molecule. The spectra were compatible, however, with a 1-cinnamoylpyrazoline unit, and structure **4** for A was confirmed by acylation of **3** with cinnamoyl chloride.[5] The formation of **4** reveals that



the rate of 1,3-dipolar addition of diazomethane to the unsaturated chloride or diazo ketone **2**, in contrast to the α-methyl derivative,[3] is comparable with the rate of acylation of diazomethane, permitting the pyrazoline **3** to compete successfully with diazomethane for acid chloride. This situation places an unfortunate restriction on the availability of α,β-unsaturated diazo ketones such as **2**.

In connection with the attempted preparation of **2**, several substituted pyrazolines were obtained from **3**. Reaction with methanolic hydrochloric acid, under conditions which generally give chloromethyl ketones,[3] gave a mixture of methoxyacetyl- and chloroacetylpyrazolines from which the former was isolated; the chloroacetyl compound was best prepared in aqueous tetrahydrofuran containing hydrochloric acid and lithium chloride. The chloro ketone was quite sensitive, and darkened rapidly on heating in solution with the formation of tarry polymeric material. Efforts to characterize products arising from cyclization to a 1,2-diazabicyclo[3.2.0]heptene derivative were unsuccessful. Attempts were also made to convert pyrazolines **3**, **4**, and **6** into the respective 3-acetylpyrazoles by oxidation with manganese dioxide or lead tetraacetate; no products could be isolated.



5 X = OCH_3
6 X = Cl
7 X = OH

Experimental Section

1-Cinnamoyl-3-diazoacetyl-4-phenyl-2-pyrazoline (4). A.—To a solution of 0.12 mol of diazomethane in ether at 0°, a solution of 9.3 g (0.056 mol) of cinnamoyl chloride in 50 ml of ether was added dropwise. After standing at 0° overnight, pale yellow crystals separated. These were collected and dried to give 2.5 g (26%) of **4**: mp 180° dec (recrystallization from methanol–tetrahydrofuran did not change the melting point); λ_{max}^{EtOH} 302 mμ (ε 31,000), 333 (25,000); ν_{KBr} 2080, 1665, 1625 cm^{-1}; δ ($CDCl_3$) 4.0–4.8 (m, 3, H-4 and H-5), 6.1 (s, 1, CHN_2), 7–8 (m, 12, aromatic and vinyl).

B.—Ether solutions of 3-diazoacetyl-4-phenylpyrazoline (**3**), 214 mg (1 mmol), and 84 mg (0.5 mmol) of cinnamoyl chloride were combined and allowed to stand. Evaporation gave 124 mg (72%) of the cinnamoylpyrazoline **4**, mp 180° dec, ir same as that from A.

A solution of **4** in methanol containing sodium methoxide was allowed to stand overnight, and the pyrazoline **3** was isolated.

1-Cinnamoyl-3-chloroacetyl-4-phenyl-2-pyrazoline.—A solution of 200 mg of the cinnamoylpyrazoline **4** in 3 ml of tetrahydrofuran was treated with 2 ml of concentrated hydrochloric acid. After gas evolution subsided, the solution was warmed briefly and then diluted with water. The resulting solid was collected and recrystallized from methanol to give colorless prisms of the title compound: mp 180°; ν_{KBr} 1700, 1660, 1620; δ ($CDCl_3$) 4.0–4.7 (m, 3), 4.7 (s, 2), 7–8 (m, 12).

Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.09; H, 4.86; N, 7.94. Found: C, 68.36; H, 4.88; N, 7.82.

Treatment of this 1-cinnamoyl-3-chloroacetylpyrazoline with 1 equiv of bromine in chloroform solution gave, after the usual

(1) Supported by Grant G.P. 5219 from the National Science Foundation.

(2) J. H. Wotiz and S. N. Buco, *J. Org. Chem.*, **20**, 210 (1955).

(3) J. A. Moore, *ibid.*, **20**, 1607 (1955).

(4) A. N. Nesmajanov, M. I. Kybinskaya and N. K. Kochetkov, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*, 1197 (1956); *Chem. Abstr.*, **51**, 5727 (1957).

(5) NOTE ADDED IN PROOF.—In a paper which became available to us after this note was submitted, M. Itoh and A. Sugihara, *Chem. Pharm. Bull.*, **17**, 2105 (1969), report a similar conclusion about **4**. Our findings agree in all respects with those of Itoh and Sugihara.

isolation procedure, 440 mg (85%) of **1-(2,3-dibromo-3-phenylpropionyl)-3-chloroacetyl-4-phenyl-2-pyrazoline**: mp 183–185° (recrystallized from methanol); δ ($CDCl_3$) 4.1–4.7 (m, 3), 4.7 (s, 2), 5.63, 5.88 (dd, 2, AB, $|J_{AB}| = 11.5$ Hz), 7.2–7.5 (m, 10).

Anal. Calcd. for $C_{20}H_{17}Br_2ClN_2O_2$: C, 46.86; H, 3.34. Found: C, 46.92; H, 3.49.

3-Methoxyacetyl-4-phenyl-2-pyrazoline (5).—A solution of 1.07 g of **3** in 20 ml of methanol was treated with 2 ml of 1 *N* methanolic hydrochloric acid. After gas evolution ceased, the solution (two spots on tlc) was diluted with water. After extraction, etc., evaporation of the ether gave 260 mg of colorless crystals, mp 115–118°. Two recrystallizations from ether–petroleum ether gave needles of **5**: mp 120–122°; ν_{KBr} 1650 cm^{-1}; δ ($CDCl_3$) 3.4 (s, 3), 3.4–4.5 (m, 3), 4.5 (apparent doublet, 2-Hz separation, probably center of AB dd), 6.8 (s, 1, NH), 7.2 (s, 5).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.59; N, 12.84. Found: C, 65.84; H, 6.25; N, 12.94.

3-Chloroacetyl-4-phenyl-2-pyrazoline (6).—To a solution of 1.07 g of **3** and 2.1 g of LiCl in 10 ml of THF and 5 ml of water was added 4.5 ml of 1 *N* hydrochloric acid. The two-phase mixture was stirred for 2 hr and then extracted, etc. Evaporation gave 0.8 g of white solid still containing an ir peak at 2080 cm^{-1}. Crystallization from ether–pentane gave crystals of **6**: mp 97° (darkening at 60°); one spot tlc (corresponding to faster moving spot in tlc of reaction mixture from **5**); δ ($CDCl_3$) 3.3–4.5 (m, 3), 4.5 (apparent doublet), 6.75 (s, 1, NH), 7.2 (s, 5). Analytically pure material was not obtained since prolonged drying caused decomposition.

Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.82; H, 4.92; N, 12.12.

The hydroxyacetylpyrazoline **7** was prepared from **3** in aqueous THF plus 1 *N* sulfuric acid. A viscous oil was obtained. After purification on a 20 × 20 cm, 2-mm-thick silica gel plate ($CHCl_3$–MeOH 23:2), the product remained an oil. Treatment with phenyl isocyanate gave the **N-phenylcarbamate ester of 1-N-phenylcarbamoyl-3-hydroxyacetyl-4-phenylpyrazoline**: mp 257°; ν_{KBr} 3100, 1720, 1660 cm^{-1}.

Anal. Calcd for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 67.86; H, 5.01; N, 12.66. Found: C, 67.65; H, 5.16; N, 12.44.

Registry No.—**2**, 24265-71-2; **3**, 24265-72-3; **4**, 24265-73-4; **5**, 24265-74-5; **6**, 24265-75-6; 1-cinnamoyl-3-chloroacetyl-4-phenyl-2-pyrazoline, 24265-76-7; 1-(2,3-dibromo-3-phenylpropionyl)-3-chloroacetyl-4-phenyl-2-pyrazoline, 24265-77-8; N-phenylcarbamate ester of 1-N-phenylcarbamoyl-3-hydroxyacetyl-4-phenylpyrazoline, 24265-78-9.

Reaction of 6,6-Dihalobicyclo[3.1.0]hexanes with Morpholine[1]

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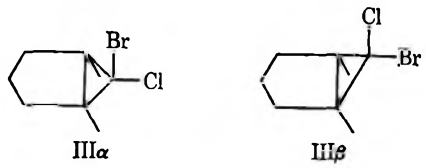
No reports appear in the literature covering the reaction of *gem*-dihalobicyclo[3.1.0]hexanes with amines to give N-substituted derivatives. This report describes the reactions of morpholine with the 6,6-dibromo- (I), 6,6-dichloro- (II), and 6-bromo-6-chlorobicyclo[3.1.0]hexanes (III) at 128°.

Compound I readily reacted with morpholine at 128° in 5 min to give a heavy precipitate of morpholine hydrobromide and 2-bromo-3-morpholinocyclohexene (IV). Compound II had to be heated for 24 hr before reacting entirely to give 2-chloro-3-morpholinocyclohexene (V).

Compound III exists in two isomeric forms, α and β.



IIIα IIIβ

In an earlier brief report[2] it was indicated that the α and β isomers react stereospecifically with aqueous silver nitrate to give from one isomer only silver chloride and 2-bromo-3-hydroxycyclohexene and from the other isomer only silver bromide and 2-chloro-3-hydroxycyclohexene.

It was now of interest to determine whether these isomers again would exhibit the same stereospecificity in their reaction with morpholine and to determine the products of this reaction.

Compound III was prepared by adding dibromochloromethane to a mixture of cyclopentene and potassium *t*-butoxide at 0°. Crude III was purified by vacuum distillation at temperatures low enough to avoid thermal rearrangement[3,4] to the bromochlorocyclohexenes. The ir spectrum and bromine unsaturation tests indicated the absence of unsaturation.

Reaction of III with refluxing morpholine (118°) for 5 min gave an exothermic reaction and the precipitation of morpholinehydrobromide. Quenching of the reaction with water and neutralizing with hydrochloric acid afforded 46% V and 32% the less reactive isomer IIIβ. The rapid reaction of the reactive isomer of III with morpholine was similar to the reactivity of I under identical conditions.

The unreactive isomer was obtained by fractional distillation and its purity was ascertained by the vpc and ir and nmr spectra. The ir spectrum of the unreactive isomer lacked the following peaks present in the mixture of isomers: 10.52, 10.87, 11.77, 12.75, and 13.33 μ. Further spectral details are described in Table I. The nmr of the unreactive isomer also lacked a peak at δ 2.05 which was present in the nmr of the mixture of IIIα and IIIβ. Reaction of this isomer with morpholine at 128° gave no immediate reaction as determined by vpc analysis. After 24 hr the reaction was complete and afforded 62% IV. The reactivity of this isomer was similar to the reactivity of II with morpholine.

In the study of the epimeric 7-chlorobicyclo[4.1.0]-heptanes, cristol and coworkers[5] suggested that the loss of the halide ion *trans* to the hydrogen atoms at C-2 and C-4 is preferred by a large factor. Schleyer[6] has observed a similar order of reactivity in the solvolysis of the epimeric monotosylbicyclo[4.1.0]heptanes. Cristol further reasoned that, on the basis of the rates of solvolysis (carried out at 124.6° in glacial acetic acid–sodium acetate), the same halogen leaves in 7,7-bicyclo[4.1.0]heptane.

(1) For the previous paper on the reaction of *gem*-dibromocyclopropanes with morpholine, see S. R. Sandler, *J. Org. Chem.*, **33**, 4537 (1968).

(2) P. S. Skell and S. R. Sandler, *J. Amer. Chem. Soc.*, **80**, 2024 (1958).

(3) S. R. Sandler, *Chem. Ind.* (London), 1481 (1968).

(4) S. Winstein and J. Sonnenberg, *J. Org. Chem.*, **27**, 748 (1962).

(5) S. J. Cristol, R. M. Sequeira, and C. H. DePuy, *J. Amer. Chem. Soc.*, **87**, 4007 (1965).

(6) P. von R. Schleyer, G. W. Van Dine, U. Schollkopf, and J. Paust, *ibid.*, **88**, 2868 (1966).

TABLE I
ELEMENTAL AND SPECTRAL ANALYSIS OF THE NEW PRODUCTS

Compound	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Nmr spectral data,[a] δ
III (α and β)	36.80	4.09	37.07	4.30	Complex at 1.85, 2.05, and 2.15 (CH_2 and CH groups in the cyclopentane ring)
IIIβ	36.80	4.09	36.98	4.27	Complex at 1.85 and 2.15 (CH_2 and CH groups in the cyclopentane ring)
IV	50.09	6.78	49.91	6.62	Complex at 1.75 and 1.95 (CH_2 groups in cyclohexene ring) complex at 3.2 (>CHN–), complex at 6.2 (–CH=CBr), and characteristic absorption for the morpholine hydrogens
V	59.50	7.94	59.83	7.94	Complex at 1.68 and 2.0 (CH_2 groups in the cyclohexene ring), complex at 3.15 (>CHN–), complex at 5.94 (–CH=CBr), and characteristic absorption for the morpholine hydrogens

[a] The integrated spectra were consistent with the assigned structure.

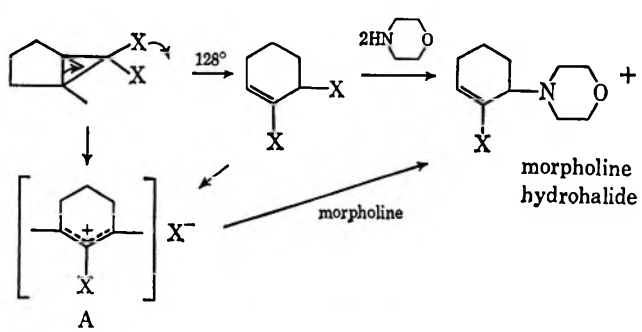
TABLE II
THE THERMAL RING-OPENING REACTION OF 6,6-DIHALOBICYCLO[3.1.0]HEXANES IN THE PRESENCE OF MORPHOLINE

gem-Dihalocyclopropane	Morpholine, mol	Temp, °C	Time, hr	Product[a]	Yield, %	Bp (mm), °C	n_D
I (0.100)	0.200	128	0.25	IV	100	132 (4.0)	1.5383 (20°)
II (0.177)	0.400	128	24	V	45	118 (4.0)	1.5141 (25°)
IIIα and IIIβ (0.120)	0.240	128	1/12	V	46	88 (0.5)	1.5178 (25°)
				Unreacted isomer (IIIβ)	32	35 (1.0)	1.5241 (25°)
IIIβ, (0.0368, unreactive isomer)	0.200	128	24	IV	62	95 (0.5)	1.5360 (26°)

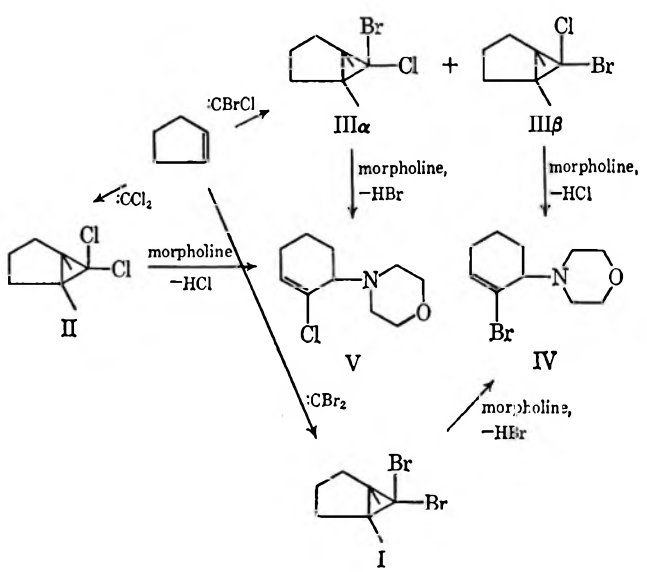
[a] The glpc analyses of the products were obtained on an 8.5-ft column packed with 25% silicone DC 200 on Celite at concentration *P* obtained from The Burrell Corp., Pittsburgh, Pa.

The above data suggests that the stereochemical assignment of the reactive isomer is IIIα. This isomer should lose Br^- at a rate similar to that of I, whereas the unreactive isomer IIIβ should lose a Cl^- at a rate similar to that of II. These conclusions are in line with the observed rates of these isomers.[2] The experimental data is briefly summarized in Scheme I.

Possible mechanisms of this reaction may either involve prior thermal ring opening at 128° to β-haloallyl halides which subsequently react with morpholine to give the observed products or the intermediate formation of carbonium ion A which undergoes a nucleophilic attack by morpholine.



SCHEME I



Strong evidence exists in the literature[4,7] to support the thermal ring opening reaction of I and other *gem*-dihalocyclopropanes.[3]

Experimental Section[8]

The dihalocarbene adducts were generally prepared by a procedure similar to those described earlier.[9-11] The procedure for the thermal ring-opening reaction of substituted *gem*-dihalocyclopropanes in the presence of morpholine is similar to that described in a previous paper.[1] The preparation of III has not been described before and is briefly given below.

6-Bromo-2-chlorobicyclo[3.1.0]hexane (III).—To a cooled (0–10°) flask containing 27.2 g (0.40 mol) of cyclopentene, 150 ml of pentane, and 33.6 g (0.30 mol) of potassium *t*-butoxide was added dropwise 41.70 g (0.20 mol) of dibromochloromethane (Dow). After the addition the reaction was stirred for 2–3 hr at room temperature, water was added, and the organic layer was separated, washed, dried, and concentrated. The residue upon vacuum distillation yielded 65% III, bp 53° (2.0 mm), n^{25}D 1.5257–1.5298. The analysis and spectral data is described in Table I.

Tables I and II describe the details of the thermal ring-opening reaction of 6,6-dihalobicyclo[3.1.0]hexanes with morpholine at 128°.

Registry No.—Morpholine, 110-91-8; I, 2568-36-7; II, 23595-96-2; IIIα, 23595-97-3; IIIβ, 23595-98-4; IV, 23595-99-5; V, 23596-00-1.

Acknowledgment.—The author wishes to express his appreciation to Professor Daniel Swern of Temple University, Philadelphia, Pa., for his generous help in obtaining all of the nmr spectra.

(7) L. Gatlin, R. E. Glick, and P. S. Skell, *Tetrahedron*, **21**, 1345 (1965).

(8) (a) The elemental analyses were obtained by Dr. Stephen M. Nagy, Belmont, Mass. (b) Melting and boiling points are uncorrected. The nmr spectra (neat) were recorded on a Varian A-60A spectrometer and the δ values are in parts per million from tetramethylsilane.

(9) W. von E. Doering and A. K. Hoffman, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

(10) P. S. Skell and A. Y. Garner, *ibid.*, **78**, 3409 (1956).

(11) P. S. Skell and A. Y. Garner, *ibid.*, **78**, 5430 (1956).

Reactions of Chlorine and Iodobenzene Dichloride with Cyclodecenes[1]

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Additions to medium-ring olefins have led to data of considerable significance for reaction mechanisms.[3,4] Both vicinal and transannular addition products have been obtained, and transannular processes may dominate the overall reaction.[3,4] Halogen additions to olefins have received much attention and have been shown to proceed by both cationic and radical pathways,[5] but few halogen additions to medium-ring cycloalkenes have been reported.

Bromine adds to *cis*-cyclodecene in carbon tetrachloride at −10° to form both *trans*-1,2-dibromocyclodecane (10% yield) and *cis*-1,6-dibromocyclodecane (40% yield), as well as other components in a complex mixture.[4d,e] Only the transannular product, *trans*-1,6-dibromocyclodecane, has been identified in the product mixture obtained from *trans*-cyclodecene under the same conditions.[4d] Both bromine[6] and chlorine[4a,7] add normally to *cis*-cyclooctene to produce *trans*-1,2-dihalocyclooctanes.

We report here an investigation of the reactions of chlorine and of idobenzene dichloride,[8] both under ionic and radical conditions,[5,8] with the isomeric cyclodecenes. Product-distribution data have been obtained and are summarized in Table I.

The production of a single, vicinal addition product in the reaction of *cis*-cyclodecene with chlorine, under both ionic and radical conditions, contrasts surprisingly with the predominant formation of the transannular addition product when bromine[4d,e] or iodobenzene dichloride is the reactant. Although we do not yet have enough energy data to have predicted these results with any confidence, the precise course of these halogen additions undoubtedly depends on a delicate balance of energy requirements among competing pathways. The energy requirements for product formation from a 2-chlorocyclodecyl intermediate (cation or radical) and chlorine is lower than that for reaction of the intermediate with iodobenzene dichloride (or bromine) and for transannular hydrogen shift. With iodobenzene dichloride or bromine as reactant, transannular hydrogen shift in the intermediate is favored over direct product formation.[9]

No vicinal dichloride was obtained from *trans*-cyclodecene reacting with either chlorine or iodobenzene dichloride. The greater internal strain in the *trans*-cyclodecene compared with the *cis* isomer may be wholly responsible for the occurrence of transannular hydrogen shifts, but geometry may be an important factor, also. Examination of a Dreiding molecular model of *trans*-cyclodecene indicates that one side of the C=C π cloud is effectively blocked by the chain of methylene groups in the ring, and, without severe conformational change, the initially formed intermediate would not be likely to form vicinal product by *anti* addition. The large amount of 3-chloro-1-cyclodecene formed from *trans*-cyclodecene, compared with that from *cis*-cyclodecene, probably is related in a similar fashion to the conformations of the olefins.

Dechlorination of the *trans*-1,2-dichlorocyclodecane

(1) (a) Based on the Ph.D. Dissertation of D. B. S., Louisiana State University, 1969. The financial assistance from the Charles E. Coates Memorial Fund, donated by George H. Coates, for preparation of the Ph.D. Dissertation of D. B. S. is gratefully acknowledged. (b) Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968, paper number 39.

(2) National Aeronautics and Space Administration Trainee, 1964–1966.

(3) For reviews of medium ring chemistry, including some additions to olefins, see (a) V. Prelog and J. G. Traynham, in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 9; (b) A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.* (London), **20**, 148 (1966).

(4) (a) J. G. Traynham and T. M. Couvillon, *J. Amer. Chem. Soc.*, **89**, 3205 (1967); (b) M. Fisch and G. Ourisson, *Chem. Commun.*, 407 (1965); (c) J. G. Traynham, G. F. Franzen, G. A. Knesel, and D. J. Northington, Jr., *J. Org. Chem.*, **32**, 3285 (1967); (d) J. Sicher, J. Zavada, and M. Svoboda, *Collect. Czech. Chem. Commun.*, **27**, 1927 (1962); (e) M. Havel, M. Svoboda, and J. Sicher, *ibid.*, **34**, 340 (1969). (We acknowledge with gratitude the receipt of a prepublication copy of this paper from Professor Sicher.)

(5) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 2161 (1965).

(6) A. C. Cope and G. W. Wood, *ibid.*, **79**, 3885 (1957).

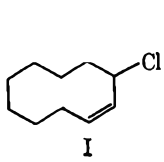
(7) (a) E. A. Forbes, B. R. Gofton, R. P. Goughton, and E. S. Waight, *J. Chem. Soc.*, 4711 (1957); P. W. Havinga, *Rec. Trav. Chim. Pays-Bas*, **81**, 1053 (1962).

(8) D. D. Tanner and G. C. Gidley, *J. Org. Chem.*, **33**, 38 (1968).

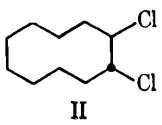
(9) A substantial difference in the composition of the dihalocyclopentane product mixtures formed from bromine and chlorine additions to bicyclo[2.1.0]pentane has been reported: R. T. LaLonde, *J. Amer. Chem. Soc.*, **87**, 4217 (1965).

TABLE I

PRODUCT CONVERSIONS FROM CHLORINATIONS OF CYCLODECENES[a]



I



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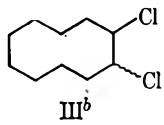
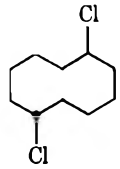
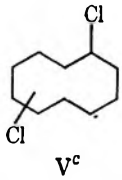


III[b]



IV



V[c]

				Vicinal		Transannular	
Cyclodecene	Reagent	Condition[d]	I	II	III	IV	V
cis	Cl_2	Ionic	13	63			
cis	Cl_2	Radical	22	29			
trans	Cl_2	Ionic	39			5	13
trans	Cl_2	Radical	43			9	9
cis	$C_6H_5ICl_2$	Ionic	10		8		24
cis	$C_6H_5ICl_2$	Radical	6				45
trans	$C_6H_5ICl_2$	Ionic	46			10	3
trans	$C_6H_5ICl_2$	Radical	31				32

[a] Per cent. Based on starting cyclodecene, some of which was not converted into products and was removed with solvent during rotary evaporation. [b] Vicinal dichloride identified from nmr spectrum of mixture; probably *trans*, but stereochemistry not established. [c] One or more transannular dichlorides (1,4-, 1,5-, and/or 1,6-), identified from nmr spectrum. [d] Conditions for chlorination, ionic or radical; see Experimental Section for details.

product with zinc dust in refluxing ethanol gave a mixture of cyclodecenes (78% *trans* and 22% *cis*).[10a] Both *anti*[10b] and *syn*[4e] eliminations of bromine by zinc dust have been reported; in the 10-membered ring, *syn* elimination appears to be the preferred process for both debromination and dechlorination. It is important to note that vicinal chlorine addition to *cis*-cyclodecene (no zinc or zinc chloride) is an *anti* process (*trans*-1,2-dichloride), but zinc- and iodide-promoted dechlorinations of the dichloride are predominantly *syn*.

Experimental Section

For gas chromatography, a Beckman Model GC-5 instrument equipped with a thermal conductivity detector and a 12 ft × 1/8 in. column packed with 5% Carbowax 20M on 60–80 mesh Chromosorb P was used. Nuclear magnetic resonance (nmr) data were obtained with Varian Model A-60A and HA-100 instruments with the assistance of Mr. W. Wegner, and chemical shifts are reported in parts per million relative to tetramethylsilane internal reference (negative sign indicates downfield). Infrared (ir) spectra were recorded on a Perkin-Elmer Model 137 instrument. Melting points were obtained with a Thomas–Hoover apparatus and are uncorrected. Element microanalyses were performed by Mr. R. Seab in these laboratories and are reported as the average of three determinations.

Molecular Chlorine Additions.—For 10 min, oxygen (for ionic conditions)[5] or nitrogen (for radical conditions)[5] was admitted through a sintered-glass dispersion tube and bubbled vigorously into a solution of cyclodecene[11] (0.05 mol) in carbon tetrachloride (100 ml) in a 38 × 200 mm test tube. For the radical reaction, the solution was irradiated with a clear 150-W light placed 4 in. from the test tube. The gas flow (O_2 or N_2) was maintained while chlorine gas (0.05 mol; Matheson, 99.5% purity), which had been passed through concentrated sulfuric acid, was bubbled into the solution. Hydrogen chloride was evolved during the reaction.[12] After the chlorine flow had been discontinued, the flow of O_2 or N_2 was continued for 30 min longer to sweep out any remaining HCl and Cl_2. The solvent and unreacted cyclodecene were removed by rotary evaporation, and the product mixture was distilled at reduced pressure. The distillate fractions were examined by ir and nmr techniques and were identified as 3-chloro-1-cyclodecene, *trans*-1,2-dichlorocyclodecane, *trans*-1,6-dichlorocyclodecane, and other nonvicinal dichlorocyclodecanes.[13] Table I summarizes the product distribution data.

In a representative experiment, distillation of the product mixture obtained from *cis*-cyclodecene gave two fractions, A [bp 51–55° (0.15 mm), 1.09 g], and B [bp 71–83° (0.15 mm), 6.55 g]. Element analyses (within 0.3% of calculated values for C and H) and nmr spectra revealed that fraction A was essentially pure 3-chloro-1-cyclodecene (13% yield) and fraction B was essentially pure *trans*-1,2-dichlorocyclodecane (63% yield). In like fashion, distillation of the product mixture from *trans*-cyclodecene gave two fractions, C [bp 35–38° (0.10 mm), 3.40 g], identified as 3-chloro-1-cyclodecene (39% yield), and D [bp 63–66° (0.10 mm), 2.00 g], which partially crystallized on standing. The solid (0.56 g) was recrystallized from hexane: mp 101–103°. It was subsequently identified by element analysis, nmr spectrum, and derivitization as *trans*-1,6-dichlorocyclodecane (IV, 5% yield). The liquid portion of D (1.44 g) gave an nmr spectrum with an A:B:X proton ratio of 8:8:2, indicative of transannular dichlorides.[4a] Thin layer chromatography with hexane solvent on silica gel plates activated at 120° immediately before use revealed two components in the liquid fraction in a ratio of 9:1.

Reaction of chlorine with *trans*-cyclodecene (but not with *cis*-cyclodecene) formed 0.5 g of a white, flocculent solid, which crystallized from chloroform–methanol to give colorless needles not melting below 330°. *Anal.* Found: C, 65.00; H, 11.05.

(10) (a) Dechlorination of *trans*-1,2-dichlorocyclodecane with potassium iodide in refluxing Cellosolve (50 hr, 88% conversion) produced a mixture of 90% *trans*- and 10% *cis*-cyclodecene (T. M. Couvillon, Ph.D. Dissertation, Louisiana State University, 1966, p 82). In the cyclohexane system, elimination of bromine by potassium iodide has been shown to be more stereoselective (*anti*) than elimination by zinc dust.[10b] (b) C. L. Stevens and J. A. Valicenti, *J. Amer. Chem. Soc.*, **87**, 838 (1965).

(11) *cis*- and *trans*-cyclodecene were prepared as described by J. G. Traynham, D. B. Stone, and J. L. Couvillion, *J. Org. Chem.*, **32**, 510 (1967). Reevaluation of the stereoselective dehydrochlorinations of chlorocyclodecane revealed that the predominant olefin comprises 93–94% of the product mixture.

(12) The exit gas reacted with aqueous silver nitrate to form a white precipitate and turned wet blue litmus paper red, but it did not affect wet starch–iodide paper.

(13) (a) Vicinal and nonvicinal dichlorides are readily distinguished from each other by the ratio of signals for $ClCCH_2$ and for $CH_2CH_2CH_2$ in the nmr spectrum of the product.[4a] (b) No evidence for the presence of any other chlorocyclodecenes was obtained, and the nmr spectra appear to exclude isomers of I within the detection limits of the nmr spectrometer. (c) The products do not interconvert readily. Under the conditions of these experiments, neither Cl_2 nor HCl added to 3-chloro-1-cyclodecene. Dichlorocyclodecanes decomposed during attempted gas chromatography, but they appeared to be stable to the chlorination reaction conditions.

This solid is insoluble in benzene, carbon tetrachloride, and chloroform and is assumed to be a low molecular weight polymer containing chlorine.

Ionic Reaction of Iodobenzene Dichloride[8] with Cyclodecenes.—For 10 min oxygen was admitted through a sintered-glass dispersion tube and bubbled into a solution of cyclodecene (0.05 mol) in carbon tetrachloride (30 ml), iodobenzene dichloride (0.05 mol) was added to the solution, and the oxygen flow was continued until the insoluble iodobenzene dichloride had disappeared (approximately 36 hr). Hydrogen chloride was evolved during the reaction. The solvent was removed by rotary evaporation, the product mixture was distilled at reduced pressure, and the distillate fractions were examined by ir and nmr techniques. Table I summarizes the product distribution data. Some of the distillate fractions were mixtures; a low-boiling fraction contained isomeric chloroiodobenzenes[8] as well as 3-chloro-1-cyclodecene, and the dichlorocyclodecane fraction from *cis*-cyclodecene was a mixture of vicinal and transannular dichlorides.[13] These mixtures were not separated satisfactorily, but they were readily analyzed by nmr spectroscopy.

Radical Reaction of Iodobenzene Dichloride[8] with Cyclodecenes.—A mixture of cyclodecene (0.05 mol), carbon tetrachloride (30 ml), and iodobenzene dichloride (0.05 mol), contained in a 100-ml round-bottom flask, was degassed by a freeze–thaw method to eliminate molecular oxygen. The flask was sealed, and the mixture was stirred with a magnetic stirrer at room temperature until the iodobenzene dichloride had disappeared (5 hr). Hydrogen chloride was evolved when the flask was opened. The mixture was worked up as described above for the ionic reaction with iodobenzene dichloride. The nmr spectrum of the dichlorocyclodecane fraction indicated that only transannular dichlorides were present.[13]

Reaction with *trans*-cyclodecene (but not with *cis*-cyclodecene) led to the formation of 1.3 g of a white, flocculant solid, which recrystallized from chloroform–methanol as needles which did not melt below 330°. This solid was not examined further.

Product Identification. 3-Chloro-1-cyclodecene distilled at 51–55° (0.15 mm): nmr ($DCCl_3$) −5.50 (2 H, C=C**H**), −4.21 (1 H, **H**CCl), −2.05 (4 H, CH_2CCl and CH_2C=C), and −1.43 (10 H, $CH_2CH_2CH_2$), all multiplets. *Anal.* Calcd for $C_{10}H_{17}Cl$: C, 69.55; H, 9.92. Found: C, 69.42; H, 10.02. The stereochemistry of the C=C was not determined.

The addition product identified as ***trans*-1,2-dichlorocyclodecane**, bp 68–72° (0.17 mm), gave an nmr spectrum ($DCCl_3$) consistent only with a 1,2 isomer:[4a] −4.36 (2 H, **H**CCl), −2.08 (4 H, **H**CCCl), and −1.57 (12 H, $CH_2CH_2CH_2$), all multiplets. The signal at −4.36 was a broad, complex one from which coupling constants could not be discerned, even with decoupling experiments. Partial dehalogenation of a sample of the dichloride with zinc dust in refluxing ethanol, and partial dehydrochlorination by potassium *t*-butoxide in dimethyl sulfoxide solution (room temperature), produced olefin (78% *trans*- and 22% *cis*-cyclodecene from zinc reaction; 1-chloro-1-cyclodeeene from potassium *t*-butoxide reaction) and left dichloride whose nmr spectrum was unchanged from that of the starting material. Since the isomeric *cis*- and *trans*-1,2-dichlorocyclodecanes are expected to undergo these elimination reactions at different rates, these results are taken to be strong evidence that a single 1,2-dichloride was formed in the addition reaction. Since ***cis*-1,2-dichlorocyclodecane** (synthesized by refluxing a mixture of *cis*-diol, excess thionyl chloride, and dioxane[14]) is a solid [mp 84.5–86.5°; nmr ($DCCl_3$) −4.96 (**H**CCl)], the addition product is *trans*-1,2-dichlorocyclodecane.

***trans*-1,6-Dichlorocyclodecane** (mp 101–103°) crystallized from a distillation fraction [bp 63–66° (0.10 mm)] from some of the chlorine additions. The nmr spectrum ($DCCl_3$) reveals an A:B:X proton ratio of 8:8:2, consistent with a 1,4-, 1,5-, or 1,6-dichloride structure.[4e] A portion of the dichloride was converted into *trans*-1,6-bis(phenylthio)cyclodecane,[4d] mp 101–103° (mixture of *trans*-1,6-dichloro- and *trans*-1,6-bis(phenylthio)-cyclodecanes, mp <93°).

Registry No.—*cis*-Cyclodecene, 935-31-9; *trans*-cyclodecene, 2198-20-1; chlorine, 7782-50-5; iodobenzene dichloride, 932-72-9.

(14) D. J. Cram, *J. Amer. Chem. Soc.*, **75**, 332 (1953).

Reactions of Phosphorus Azides with Activated Alkynes[1]

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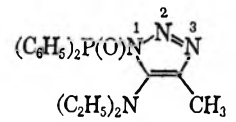
Phosphorus azides are known to add to a variety of substituted alkenes,[4–9] but there appears to be no record of studies on the reactions with alkynes, although a few condensations of some alkynes with aryl and alkyl azides have been summarized.[9,10] We wish to report that **1a** and the ynamine **2a** react in boiling benzene to

$R_2P(O)N_3$ — **1a**, $R = C_6H_5$; **b**, $R = C_2H_5O$

$R'C{\equiv}CR''$ — **2a**, $R' = (C_2H_5)_2N$; $R'' = CH_2$; **b**, $R' = C_2H_5O$; $R'' = H$



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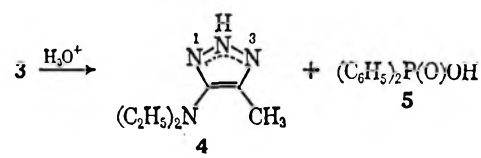
yield crystalline **3** (49%). Infrared (P→O at 8.1 μ) and nmr analyses (Table I) support the structure. Rapid hydrolytic cleavage occurred with **3** upon exposure to the atmosphere to give the triazole **4** and diphenylphosphinic acid (**5**). Acid hydrolysis gives **4** and **5** in near-quantitative yield. The broadness of the signal for the proton on nitrogen in the nmr spectrum ($CDCl_3$) of **4** suggests tautomers with the hydrogen on N-1 and N-3. Although isomers **3** and **6** are possible from reaction of **1a** and **2a**, evidence favors **3**. Several types of molecular models indicate a strong probability of nonbonded interaction between the $(C_6H_5)_2P(O)$ and $(C_2H_5)_2N$ groups in **3** and between the $(C_6H_5)_2P(O)$ and CH_3 groups in **6**, respectively. Restricted rotation around the P–N and C_6H_5–P bonds in **3** and **6** might



4 **5**

(1) We gratefully acknowledge support from the Public Health Service, Cancer Institute, Grant CA 07202-07.

(2) Research Associate, 1968–1970.

(3) Predoctoral Candidate, 1969–present.

(4) K. D. Berlin and L. A. Wilson, *Chem. Ind.* (London), 1522 (1965).

(5) K. D. Berlin and L. A. Wilson, *Chem. Commun.*, 280 (1965).

(6) K. D. Berlin and M. A. R. Khayat, *Tetrahedron*, **22**, 975 (1966); **22**, 987 (1966).

(7) K. D. Berlin, L. A. Wilson, and L. M. Raff, *ibid.*, **23**, 965 (1967).

(8) K. D. Berlin and R. Ranganathan, *ibid.*, **25**, 793 (1969).

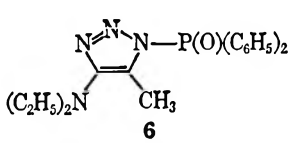
(9) F. R. Benson and W. L. Savell, *Chem. Rev.*, **46**, 1 (1950).

(10) R. Huisgen, R. Knorr, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 4014 (1965).

TABLE I
60-MHz NMR DATA FOR PRODUCTS IN δ VALUES (*J*, HERTZ)

Compd	CH_3	$=CCH_3$	CH_2	NH	ArH	CH_3	CH_2OP
3	1.03 t (7)	2.29 s	3.22 q (7)		7.46 m		
4	1.06 t (7)	2.3 s	3.21 q (7)	13.0 m br			
9	0.98 t (7)	2.2 s	3.12 q (7)			1.38 t (7)	4.25 quintet (7)

expectedly be reflected in the chemical shift and shape of nmr signals for protons in the ethyl group of **3** or in the signal for the protons on the methyl group attached to the ring in **6**. Low-temperature studies at 0, −20,



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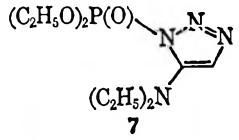

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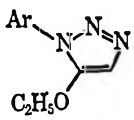

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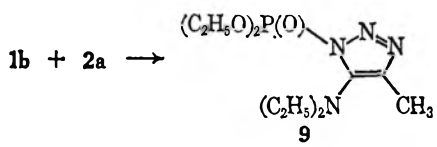
−40, and −60° at 60 and 100 MHz of **3** and **4** in CCl_4 indicate increased broadening of the signals for the protons of the ethyl group, although the effect was more pronounced in **3**. Virtually no change in δ value or shape of the singlet was observable for the methyl group on the ring in **3** or **4**. On this basis **6** is less tenable. Moreover, the mode of addition of **1a** to **2a** appears to be similar to the condensations of *para*-substituted aryl azide with ethoxyacetylene, which yielded **8** in high yield.[10]

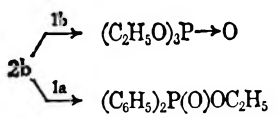
Similarly, **1b** and **2a** under identical conditions give a liquid tentatively identified by nmr as **9**, which is thermally unstable and decomposes upon attempted distillation. Chromatography of **9** over neutral alum-



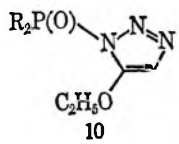
9

ina led to P–N cleavage. Condensation of **1b** and **2a** in the absence of solvent near room temperature (initial mixing near 0° for 2 hr) gave **9** which, *via* nmr (Table I) examination, appeared to be of high purity. Again, heavy decomposition of **9** ensued when distillation was tried even in a molecular still.

Ethoxyacetylene (**2b**) and **1a** or **1b** react when heated in the absence of solvent under N_2 with heavy tar formation. In benzene, the condensation is sluggish over 3–4 days with recovery of starting azides and the production of tar. Interestingly, **1b** and **2b** combine in a novel but unknown fashion to give triethyl phosphate



(33%). Likewise, tar and ethyl diphenylphosphinate result from **1a** and **2b**. Both of these data are in contrast to that reported for reaction of **2b** with ArN_3, where a triazole results.[10,11] Whether or not ethoxylation of phosphorus to give a POC_2H_5 group is at the expense of **2b** or an intermediate, such as **10**, is not



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readily discernible, since the reaction mixtures begin to darken quickly when the reagents are heated, apparently an indication of the presence of tar. Glpc analyses of both mixtures indicate very small amounts of several other products (<5% total) and suggest a complex process.

Experimental Section

Reaction of Diphenylphosphinyl Azide (1a) with 2a. Preparation of Triazole 3.—To solution of distilled **2a** (3.35 g, 0.03 mol) [obtained from Fluka AG, Buchs SG, bp 130–132° (760 mm)], in dry benzene (15 ml) was added a solution of **1a**[12] (7.30 g, 0.03 mol) in dry benzene (15 ml) over 30 min at 60–65° in a dry box under N_2. The mixture was then boiled for 3 hr. Cooling to room temperature resulted in a dark brown solution, which was diluted to turbidity with hexane and left overnight, whereupon a white solid separated. The mixture was removed from the dry box and chilled in ice; the filtered solid (5.07 g, 49%) melted at 118–120°. Recrystallization from benzene–petroleum ether gave pure **3**, mp 120.5–121.5°.

Anal. Calcd for $C_{19}H_{23}N_4OP$: N, 15.81; P, 8.74. Found: N, 15.55; P, 8.74.

Hydrolysis of Triazole 3.—The triazole **3** (354 mg, 1.0 mmol) was stirred at room temperature with 5% HCl (20 ml) for 30 min, and the mixture was poured into saturated $NaHCO_3$ solution. Ether extracts of the aqueous mixture were dried ($MgSO_4$) and the solvent was evaporated to give 150 mg (98%) of **4**. Distillation gave **4**, pure by tlc and nmr, bp 60–70° (0.25 mm).

Anal. Calcd for $C_7H_{14}N_4$: N, 36.33. Found: N, 35.94.

Acidification with dilute HCl of the aqueous mixture precipitated **5** (191 mg, 87%), identified by mixture melting point with an authentic sample.

Reaction of Diethyl Phosphorazidate (1b) with 2a.—To a solution of **2a** (2.22 g, 0.02 mol) in dry benzene (10 ml) over a 1-hr period was added **1b** (3.58 g, 0.02 mol) under N_2. The temperature rose to 44° and fell to 27° within the next 40 min. After another 0.5 hr, the solvent was removed to give 5.5 g of a dark liquid. Distillation at 120–130° (0.005 μ) resulted in extensive decomposition with a black tar produced. After the reactants were mixed and stirred at 0–10° for 2 hr under N_2, the temperature was raised to and maintained at 24–26° for another 2 hr. As in the previous experiment, the absence of the azide band at 4.61 μ in the infrared spectrum of the reaction mixture indicated a high conversion. Nmr analysis of both mixtures prior to attempted distillation was that found in Table I for **9**. Tlc of the mixture before distillation indicated several very minor impurities, and thus an elemental analysis of **9** was precluded.

Reaction of 1b with 2b.—A solution of **1b** (16.3 g, 0.1 mol) and freshly distilled **2b** (7.0 g, 0.1 mol) [obtained from Farchan Research Laboratories, bp 45–50° (749 mm),[13] nmr (neat with trace TMS) δ 1.34 (t, J = 7 Hz), 1.47 (s), and 4.06 (q, J = 7 Hz)] in benzene (20 ml) was stirred and boiled for 90 hr under N_2. The dark mixture was cooled to room temperature and then distilled. Unreacted **1b** (9.0 g, 55%) and triethyl phosphate (6.0 g, 33%) were obtained and compared with authentic samples. Glpc

(11) P. Grünanger, P. Vita Finzi, and E. Fabbri, *Gazz. Chim. Ital.*, **90**, 413 (1960).

(12) Azides **1a** and **1b** are described elsewhere.[4-8]

(13) E. R. H. Jones, G. Eglinton, M. D. Whiting, and B. L. Shaw ["Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 404] report a boiling point of 49–51° (749) mm

analysis of the remainder of the product on a 5 ft × 0.125 in. column of 10% Carbowax 20M on 80–100 mesh (DMCS), A-W revealed small amounts (<5% total) of several other products.

Reaction of 1a with 2b.—A solution of **1a** (16.9 g, 0.07 mol) and freshly distilled **2b** (10.5 g, 0.15 mol) in 25 ml of dry benzene was stirred at reflux for 4 days under N_2. Petroleum ether (bp 40–60°) was added to the mixture at room temperature, causing a black oil to separate with a solid suspended in it. Distillation of the petroleum ether–benzene gave back 4.5 g (27%) of **1a**.

The black oil was redissolved in benzene and a small amount of solid precipitated was filtered from solution. Separation and subsequent purification identified the solid as diphenylphosphinic acid. The benzene solution was distilled to give 5.0 g (34.5%) of ethyl diphenylphosphinate (based on **1a**), identified by comparison with an authentic sample.[14]

Registry No.—**3**, 23646-70-0; **4**, 23596-01-2; **9**, 23646-71-1.

(14) A general procedure for the preparation of alkyl diarylphosphinates is available; see K. D. Berlin, T. H. Austin, and M. Nagabhushanam, *J. Org. Chem.* **30**, 1267 (1965).

Autoxidation of Some Phenols Catalyzed by Ring-Substituted Salcomines

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It has been shown that salcomines (see Table I) catalyze the autoxidation of 2,6-substituted phenols selectively, to give the corresponding benzoquinones (BQ), diphenoquinones (DPQ), or polymers.[1] The selectivity of the salcomine catalysts was correlated, in a qualitative way, with the amounts of the mononuclear salcomine and its O_2-bridged dimer present in solution at equilibrium.

We studied the catalytic oxidation of 2-methyl-6-benzylphenol and 2,6-dichlorophenol using a series of ring-substituted salcomines to see whether the nature of the substituent would affect their selectivity or oxidizing power (the dichlorophenol cannot be oxidized with unsubstituted salcomines).[1] Several *stoichiometric* oxidations of 2-methyl-6-benzylphenol were carried out using the unsubstituted pyr-salcomine and varying the time at which O_2 was admitted to the system.

Experimental Section

Preparation and Properties.—The preparation and properties of all of the salcomines used in this study are described in the literature.[1-3] They are readily obtained in high purity as highly colored, crystalline solids by the reaction in aqueous solution of a cobalt salt, ethylenediamine, and pyridine with the appropriate substituted salicylaldehyde. The elemental analyses (C, H, N, Co, and halogen when present), color, and crystal form of all of the salcomines used in this study were in excellent agreement with those reported in the literature.

Oxidations. Salcomines in Catalytic Amounts.—To a mixture of 0.0005 mol of catalyst (based on the molecular weights shown in Table I) in 100 ml of chloroform was added 0.01 mol of the 2,6-substituted phenol. Oxygen was bubbled through the solutions at room temperature for 24 hr. The reaction mixtures were then filtered, diluted to 250 ml with chloroform, and analyzed as described below.

Salcomines in Stoichiometric Amounts.—The catalyst used in these oxidations was bis(salicylaldehyde)ethylenediiminepyridinecobalt(II) (Table I, entry 10), and the phenol used was 2-methyl-6-benzylphenol. Two procedures were followed.

(A) The catalyst (0.005 mol, 2.02 g) was slurried with 140 ml of $CHCl_3$ *under nitrogen*. Then 0.01 or 0.005 mol (1.98 or 0.99 g) of the phenol was added as a solution (flushed with N_2) in 130 ml of $CHCl_3$. The initial red-purple color of the slurry did not change during this time, or for 0.5 hr after the phenol was added. The heterogeneous mixture was then flushed with O_2 and within 5 sec it turned dark brown and became homogeneous. Oxygen was bubbled through the solution for a total of 24 hr, after which it was filtered, made up to 250 ml with $CHCl_3$, and analyzed as described below.

(B) The catalyst (0.005 mol, 2.02 g) was slurried with 140 ml of $CHCl_3$ *under oxygen*. The phenol (0.01 and 0.025 mol) was then added and procedure A was followed from this point on. The mixture was brownish before and after adding the phenol and became homogeneous after adding the phenol.

C. Analytical Methods.—The reaction mixtures were analyzed for products and unreacted 2,6-disubstituted phenols using methods described previously.[1]

A qualitative test for the presence of polymers was made by pipetting a few milliliters of the reaction mixture into 100 ml of methanol. The absence of a precipitate indicated that if any polymers were present they were of very low molecular weight ($[\eta] < ca.\ 0.01$ dl/g).

The 2,6-dichlorobenzoquinone could not be isolated by tlc, since it appeared to react with itself on the tlc plates to give an insoluble product. It was necessary to reduce the reaction mixture with zinc–acetic acid, acetylate the corresponding hydroquinone using acetic anhydride, and identify the resulting product from its glpc retention time, mass spectrum, and ir spectrum by comparison with authentic material.

Results and Discussion

The results of the catalytic oxidations of 2-methyl-6-benzylphenol are shown in Table II. A general trend in the conversions and oxidation products was observed in progressing from the more electron-donating groups as substituents on the phenyl rings of the salcomine catalysts to the more electron-withdrawing groups. The donor group favored higher conversions, higher yields of the BQ, and lower yields of the DPQ than the withdrawing groups. A more precise correlation between the nature of the products and the relative strengths of the donating or withdrawing groups is not possible at this time. There were no apparent correlations of the BQ to DPQ ratios with Hammett σ values. If we consider our earlier suggestion[1] that BQ's arise from reaction of the phenols with the O_2-bridged salcomine dimers and DPQ's by reaction with their mononuclear forms (in an equilibrium mixture), then our present data suggest that electron-withdrawing groups shift the equilibrium to favor the mononuclear species and the electron-donating groups favor the binuclear species. This suggestion is supported by inspection of a plot of per cent oxygenation *vs.* O_2 pressure for the 3-methoxy- and 3-nitrosalcomines.[4] At atmospheric pressure the methoxy derivative is more highly oxygenated, *i.e.*, more of it is in the O_2-bridged dimer form, than the 3-nitro derivative.

We considered the possibility that the formation of a BQ or DPQ could be determined by the oxidation potential and/or coordination geometry of either a phenol–

(1) L. H. Vogt, Jr., J. G. Wirth, and H. L. Finkbeiner, *J. Org. Chem.*, **34**, 273 (1969).

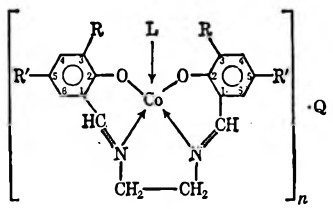
(2) R. H. Bailes and M. Calvin, *J. Amer. Chem. Soc.*, **69**, 1886 (1947).

(3) L. H. Vogt, Jr., H. M. Faigenbaum, and S. E. Wiberley, *Chem. Rev.* **63**, 269 (1963).

(4) A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1952, pp 346, 347.

TABLE I

DESCRIPTION OF THE CATALYSTS[a]



Name[b]	Registry no.	n	L	Q	R	R′	Color
Aquo-3-fluorosalcomine	23602-19-9	1	H_2O	None	F	H	Red
Pyr-3-fluorosalcomine	23602-20-2	1	Pyr	None	F	H	Red
O_2-(3-Fluorosalcomine)$_2$	23602-21-3	2	None	O_2	F	H	Black
Pyr-5-nitrosalcomine	23602-22-4	1	Pyr	None	H	NO_2	Red-brown
Pyr-3-nitrosalcomine	23602-23-5	1	Pyr	None	NO_2	H	Red-brown
Pyr-5-chlorosalcomine	23602-24-6	1	Pyr	None	H	Cl	Red-brown
Aquo-3-methoxysalcomine	18433-55-1	1	H_2O	None	OCH_3	H	Brown
Pyr-3-methoxysalcomine	23602-25-7	1	Pyr	None	OCH_3	H	Brown
O_2-(3-Methoxysalcomine)$_2$	23602-26-8	2	None	O_2	OCH_3	H	Black
Pyr-salcomine[c]	18309-20-1	1	Pyr	None	H	H	Red
O_2-Salcomine[c]	23602-28-0	2	None	O_2	H	H	Black

[a] Refer to Experimental Section for references to the preparation and characterization of the salcomines (ref 1–3). [b] The chemical names are abbreviated in the table. The complete names for these compounds are analogous to those given previously.[1] [c] Reference 1.

TABLE II

CATALYTIC OXIDATIONS OF 2-METHYL-6-BENZYLPHENOL

Catalyst	Conversion, %	BQ,[a] %	DPQ,[b] %	Ratio of BQ to DPQ
Aquo-3-fluorosalcomine[c]	66	52	61	1
Pyr-3-fluorosalcomine	39	76	29	3
Pyr-5-nitrosalcomine	20	50	21	2
Pyr-3-nitrosalcomine	7	47	53	1
Pyr-5-chlorosalcomine	53	54	42	1
Aquo-3-methoxysalcomine[c]	95	82	10	8
Pyr-3-methoxysalcomine	100	94	15	6
Pyr-salcomine	59	77	22	4

[a] 2-Methyl-6-benzylbenzoquinone. [b] 3,3′-Dimethyl-5,5′-dibenzyldiphenoquinone. [c] A duplicate experiment in which 0.4 ml (0.004 mol) of N,N,N′,N′-tetramethylethylenediamine (TMEDA) was added before adding the phenol did not result in the formation of polyphenylene ethers.

TABLE III

STOICHIOMETRIC OXIDATIONS OF 2-METHYL-6-BENZYLPHENOL[a]

Mole ratios of pyr-salcomine to phenol	O_2 Addition[b]	BQ,[c] %	DPQ,[c] %	Ratio of BQ to DPQ
2:1	After	88	19	5
2:1	Before	78	14	6
1:1	After	100	10	10
1:1	Before	95	10	10

[a] In all cases pyr-salcomine was used and 100% conversion of the phenol was obtained. [b] "After" indicates that O_2 was admitted to the system after the pyr-salcomine and phenol had been mixed in $CHCl_3$ solution. "Before" indicates that the pyr-salcomine–$CHCl_3$ mixture had been saturated with O_2 before adding the phenol. [c] See Table II, footnotes *a* and *b*, for proper names.

TABLE IV

CATALYTIC OXIDATION OF 2,6-DICHLOROPHENOL

Catalyst	Conversion, %	Products[a]
Aquo-3-fluorosalcomine[b]	55	2,6-Dichlorobenzoquinone + X
Pyr-3-fluorosalcomine	18	2,6-Dichlorobenzoquinone
Pyr-5-nitrosalcomine	20	2,6-Dichlorobenzoquinone
Pyr-3-nitrosalcomine	20	2,6-Dichlorobenzoquinone
Pyr-5-chlorosalcomine	20	2,6-Dichlorobenzoquinone + X
Aquo-3-methoxysalcomine[b]	41	2,6-Dichlorobenzoquinone
O_2-(3-Methoxysalcomine)$_2$	32	2,6-Dichlorobenzoquinone
Pyr-salcomine	No reacn	2,6-Dichlorobenzoquinone

[a] "X" indicates that a second product (red-orange in color) was detected on tlc. It moved slower than the benzoquinone; its composition was not determined. "X" was 25% by weight of the products using the aquo-3-fluorosalcomine and 44% by weight using the pyr-5-chlorosalcomine. [b] TMEDA added as in Table II, footnote c.

salcomine complex or a phenol–salcomine-O_2 complex. Thus the presence or absence of O_2 during the initial stage of the reaction could be a critical reaction variable. This hypothesis was tested by running four stoichiometric oxidations in which the molar ratio of 2-methyl-6-benzylphenol to pyr-salcomine, and the stage at which O_2 was introduced, were varied. Table III shows that addition of the O_2 before or after the phenol was added to the salcomine did not significantly affect the amounts of the BQ or DPQ produced.

That the substituents can change the oxidation potential of the catalyst is clearly evidenced by the data shown in Table IV for the oxidation of 2,6-dichlorophenol (unsubstituted salcomines do not catalyze the oxidation of the dichlorophenol). Unfortunately, there is no correlation at all between salcomines containing donating or withdrawing groups and the degree of conversions or product distributions.

Polymers were not detected in any of the reaction mixtures, and the presence of TMEDA during the oxidation did not effect polymer formation (see Table II, footnote *c*, and Table IV, footnote *b*.

Registry No.—2-Methyl-6-benzylphenol, 1208-45-3; 2,6-dichlorophenol, 87-65-0.

Acknowledgments.—We appreciate the contributions of Dr. J. V. Crivello and Dr. H. L. Finkbeiner in suggesting several possible mechanisms and experiments to explain the bahavior of the catalysts. Dr. J. R. Ladd and M. Trier prepared most of the salcomine ring derivatives. Professor M. Calvin gave us some of the difficult-to-make 3-fluorosalicylaldehyde. A. M. Toothaker isolated the acetylated 2,6-dichlorohydroquinone. Elemental analyses were performed by the Analytical Chemistry Operation of the Research and Development Center.

Kinetics of Fischer–Hepp Rearrangement

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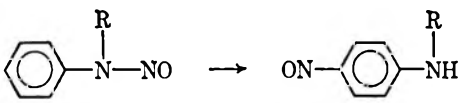
The rearrangement of aromatic nitrosamines on treatment with acids, particularly HCl and HBr, to give ring-substituted isomerides is known as the Fischer–Hepp rearrangement.[1] Although at one time



this reaction was believed to be truly intramolecular, considerable evidence accumulated in later years proved this to be untrue. Thus, when the rearrangement was carried out in the presence of urea, no C-nitroso isomeride was produced but only the secondary amine;[2] also, when the rearrangement occurs in the presence of more active foreign aromatic molecules, major transfers of the nitroso group to this molecule have been observed.[3,4] It has been found[3] that the conversion by HX occurs through the liberation of NOX, and with HCl and HBr the NO group is quantitatively removed. With sulfuric acid the yields are low, and with nitric acid no rearrangement occurs. The subsequent reaction of NOCl with the formed secondary amine to give C-nitroso compound was found to be very fast. To gain further insight into the mechanism of this reaction, a kinetic study seemed desirable, and the present work describes such a study on the hydrogen chloride catalyzed rearrangement of N-nitrosodiphenylamine to *p*-nitrosodiphenylamine.

Experimental Section

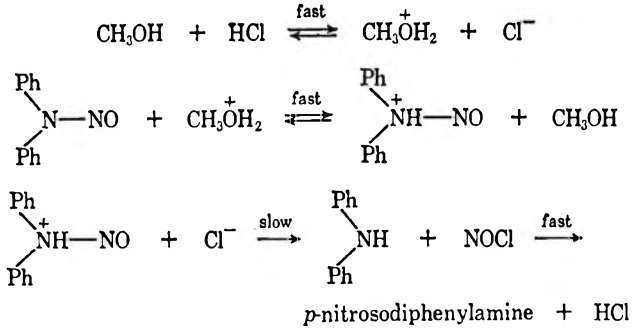
Eastman Kodak White Label compounds N-nitrosodiphenylamine and *p*-nitrosodiphenylamine were used. Analytical grade methanol and redistilled toluene were used as solvents. The solvent mixture was made up by volume. The stock solution of HCl (made by passing dry HCl into the solvent) in the desired solvent was variously diluted as required for the kinetic runs. The solution containing N-nitrosamine was mixed with the solution containing HCl in a volumetric flask thermostated at the desired temperature controlled within ±0.03°. Aliquots withdrawn at various times were quenched with methanolic sodium hydroxide, suitably diluted in methanol, and the absorbance at 430 mμ was measured in a 1-cm quartz cell on a Carl Zeiss (Models PMQ II and M4Q III) spectrophotometer to an accuracy of about 0.2%. The ultraviolet and visible spectra for both amines in methanol have been found to be similar to those reported in ethanol.[5] It has been established that the absorbance of *p*-nitrosodiphenylamine at this wavelength is linear with concentration (ϵ 16.74 × 10^3) in methanol in accordance with the Beer–Lambert law.

Results and Discussion

The rate of the reaction was found to be first order in nitrosamine and first order in hydrogen chloride at a given temperature and with a given solvent

$$\frac{-d[\text{N-nitrosamine}]}{dt} = \frac{d[\text{C-nitrosamine}]}{dt} = k_2[\text{N-nitrosamine}][\text{HCl}]$$

where k_2 is the second-order rate constant given in the last column of Table I. Arrhenius plots of log k against $1/T$ in the two solvents (not shown) are linear in the temperature range 30–50°, and the various activation parameters obtained from these plots are given in Table II.



A stepwise mechanism with a slow step involving the nucleophilic attack of chloride ion on the protonated N-nitrosamine requires third-order kinetics which are

$$\text{rate} = k_3[\text{N-nitrosamine}][\text{H}^+][\text{Cl}^-]$$

first order in each, nitrosamine, hydrogen ion, and chloride ion. Since the dependence of the rate on the concentration of chloride ion is indistinguishable from the stoichiometric concentration of molecular HCl, it seemed desirable to verify this mechanism by adding chloride ion. The results are shown in Table III where it can be seen that first-order dependence on chloride ion was not observed. The rate is still first

(1) O. Fischer and E. Hepp, *Ber.*, **19**, 2291 (1886).
(2) W. Macmillen and T. H. Reade, *J. Chem. Soc.*, 585 (1929).
(3) P. W. Neber and H. Rauscher, *Ann.*, **550**, 182 (1942).
(4) J. Glazer, E. D. Hughes, C. K. Ingold, A. T. James, G. T. Jones, and E. Roberts, *J. Chem. Soc.*, 2657 (1950).
(5) W. A. Schroeder, P. E. Wilcox, K. N. Trueblood, and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951).

TABLE I

RATE CONSTANTS FOR THE HYDROGEN CHLORIDE CATALYZED REARRANGEMENT OF N-NITROSODIPHENYLAMINE TO *p*-NITROSODIPHENYLAMINE

Temp, °C	Solvent	[N-nitrosamine], mol l.$^{-1}$	[HCl], mol l.$^{-1}$	$-$d[N-nitrosamine]/dt 10^6 mol l.$^{-1}$ sec^{-1} [a]	10^4k_2,[b] l. mol^{-1} sec^{-1}
30.00	Methanol	0.1033	0.169	1.76	1.03
		0.0517	0.169	0.881	1.04
	Toluene + methanol (3:1 v/v)	0.0507	0.148	2.70	3.60
		0.0254	0.074	7.00	3.73
40.18	Methanol	0.1033	0.194	5.02	2.79
		0.0517	0.194	2.58	2.80
		0.0310	0.194	1.55	2.86
		0.0826	0.213	4.33	2.78
		0.1022	0.115	3.07	2.81
		0.1022	0.229	5.85	2.79
		0.1022	0.0687	1.85	2.81
		0.1022	0.183	4.72	2.78
	Toluene + methanol (3:1 v/v)	0.0507	0.231	5.55	5.91
		0.0254	0.116	1.50	5.81
		0.0152	0.185	1.32	5.77
50.00	Methanol	0.031	0.0537	1.02	6.89
		0.01033	0.0716	0.433	6.72
	Toluene + methanol (3:1 v/v)	0.0254	0.083	1.58	8.95
		0.0254	0.083	1.60	9.15

[a] The absorbance of *p*-nitrosodiphenylamine at 430 mμ under acidic conditions was found to decrease slowly over a period of time, perhaps owing to some change in molecular structure. This being the case, the rate constants were obtained from initial rates by plotting [N-nitrosamine] against t. The quantity in this column represents the slope of this plot at $t = 0$. [b] In evaluating this constant, the concentrations in columns 3 and 4 have been corrected for thermal expansion of the solvent. For each run, the concentration of N-nitrosamine at $t = 0$ used to evaluate k_2 is slightly lower than that shown in column 3 since some of the N-nitrosamine will already have been converted to C-nitrosamine when the first reading was taken.

order with respect to HCl for different concentrations in the presence of added chloride ion. The slight increase in rate by chloride ion can reasonably be attributed to a salt effect. A stepwise mechanism, therefore, seems unlikely for this rearrangement.

TABLE II

ACTIVATION PARAMETERS FOR THE HYDROGEN CHLORIDE CATALYZED REARRANGEMENT OF N-NITROSODIPHENYLAMINE TO *p*-NITROSODIPHENYLAMINE

Solvent	log A, l. mol^{-1} sec^{-1}	E_A, cal mol^{-1}	$\Delta S^{\pm}$, cal deg^{-1} mol^{-1}
Methanol	9.1	18,140 ± ~600	−19.0 ± ~2.0
Toluene + methanol (3:1 v/v)	2.9	8,750 ± ~600	−47.0 ± ~2.0

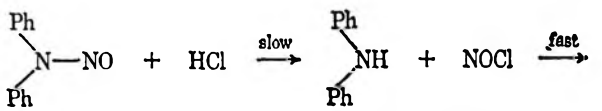
TABLE III

EFFECT OF LITHIUM CHLORIDE ADDITION ON RATE CONSTANTS FOR THE HYDROGEN CHLORIDE CATALYZED REARRANGEMENT OF N-NITROSODIPHENYLAMINE TO *p*-NITROSODIPHENYLAMINE IN METHANOL AT 50.00°[a]

[HCl], mol l.$^{-1}$	[LiCl], mol l.$^{-1}$	$-$d[N-nitrosamine]/dt, 10^6 mol l.$^{-1}$ sec^{-1}	10^4k_2, l. mol^{-1} sec^{-1}
0.175	0	2.25	6.94
0.154	0.113	2.32	8.10
0.0765	0.113	1.19	8.24
0.154	0.225	2.70	9.37
0.0765	0.225	1.35	9.35
0.162	0.338	3.27	10.8
0.176	0.450	4.03	12.3
0.0306	0.450	0.708	12.1

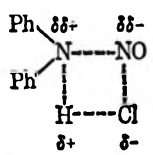
[a] [N-nitrosamine] = 0.02075 mol l.$^{-1}$ for all runs. Footnotes of Table I apply to columns 3 and 4.

The results can be accommodated by a concerted mechanism



p-nitrosodiphenylamine + HCl

with a cagelike transition state for the slow step.



Since a cyclic transition state is formed from noncyclic reactants, a negative $\Delta S^{\pm}$ is to be expected due to the restricted free rotation about the single bonds in this transition state. In addition, there may be contribution arising from charge separation whose value depends strongly on the solvent. The observed $\Delta S^{\pm}$ in methanol, −19.0 cal deg^{-1} mol^{-1}, and its considerable decrease to −47.0 cal deg^{-1} mol^{-1} in toluene + methanol are consistent with this picture. The slight increase in rate with added chloride ion might arise from a salt effect similar to that known for a reaction between neutral molecules forming a dipolar transition state.[6] The specificity of HCl and HBr in the Fischer–Hepp rearrangement, unlike other acids, can be attributed to the facile elimination of the NO group as NOX from a cagelike transition state.

Registry No.—N-Nitrosodiphenylamine, 86-30-6.

(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 186.

Mass Spectral Decompositions as a Guide to Hitherto Unrealized Reactions in Solution. Ketene Addition to the α-Methoxybenzyl Carbonium Ion

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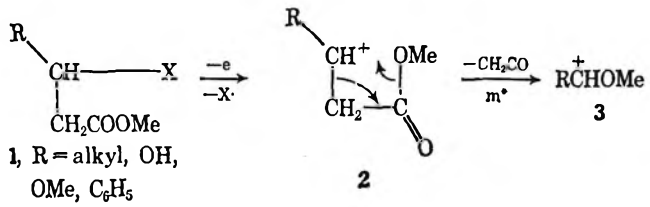
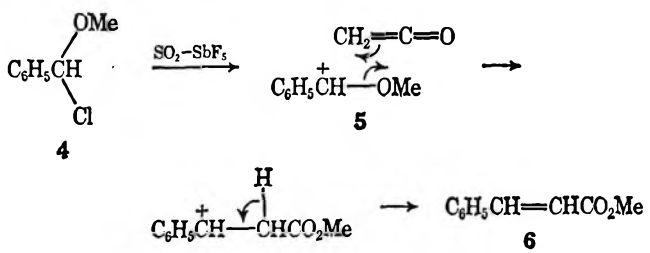
Received December 1, 1969

Carbonium ions of the general formula **2** may be generated upon electron impact from compounds **1** when X is lost as a radical (*e.g.*, X = Br, $COOCH_3$). It has been shown[1,2] that the lowest energy pathway for unimolecular decomposition of the carbonium ions is *via* loss of ketene in a process involving methoxy-group migration (**2** → **3**).



On the basis of the unimolecular gas-phase elimination of ketene from the carbonium ions **2**, we reasoned that the energy of activation of the back-reaction might also be relatively low, *i.e.*, that ketene addition to a α-methoxycarbonium ion, with associated methoxy-group migration, might be realized in a bimolecular reaction in solution.

The α-methoxybenzyl carbonium ion (**5**) was generated by addition of α-methoxybenzyl chloride (**4**)[3] to an SO_2–SbF_5 mixture at −70°;[4] formation of **5** was established by nmr spectroscopy. Approximately 1 equiv of ketene was passed through the solution at this temperature and the resulting mixture was quenched with ethanol. Standard isolation techniques gave a 12% yield of methyl cinnamate (**6**) and only 3% ethyl cinnamate.



The gas-phase and solution reactions involving the methoxy migration are represented as concerted only for convenience, and a stepwise process is not excluded.

This example demonstrates that unimolecular decompositions of positive ions in the mass spectrometer may on occasions serve as a guide to the reverse bimolecular reactions of carbonium ions in solution.

(1) I. Howe and D. H. Williams, *J. Chem. Soc., C*, 202 (1968).
(2) R. G. Cooks, J. Ronayne, and D. H. Williams, *ibid.*, 2601 (1967).
(3) F. Straus and H. Heinze, *Ann.*, **493**, 203 (1932).
(4) G. A. Olah and J. M. Bollinger, *J. Amer. Chem. Soc.*, **89**, 2993 (1967).

Experimental Section

Generation of α-Methoxybenzylcarbonium Ion.—In a typical experiment, 1.0 g of α-methoxybenzyl chloride (6.4 mmol) was added carefully to the surface of a solution of 2.0 g of SbF_5 (9.2 mmol) in 2 ml of SO_2 at −70°.[4] When the methoxybenzyl chloride had had sufficient time to cool to −70° (about 5 min), the reaction vessel was shaken to give a clear, deep red, homogeneous solution. The nmr spectrum of this solution, run at −58° on a Varian HA 100-MHz instrument, established the specific formation of the α-methoxybenzylcarbonium ion: τ 5.13 (s, 3), 1.75–2.20 (m, 5), 0.67 (s, 1).

Reaction of the Carbonium Ion with Ketene.—Approximately 1 equiv of ketene, generated by the pyrolysis of acetone, was passed through the carbonium ion solution at −70° over a period of 10 min. The product was quenched by pouring into 5 ml of ethanol at −70°; the mixture was then poured into 25 ml of water and continuously extracted with ether. The ether extract was analyzed by gas chromatography using a 4-ft LAC column at 155°, and two peaks having retention times identical with those of methyl and ethyl cinnamates were collected. The nmr and mass spectra (AEI-MS9 instrument with heated inlet) of these two fractions were identical with the corresponding spectra of the authentic esters. The yields, based on α-methoxybenzyl chloride, were 12% methyl and 3% ethyl cinnamate.

Registry No.—**5**, 23790-70-7.

The Effect of Solvents with Basic Oxygen in Epoxidation with Organic Peroxy Acids

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Received September 3, 1969

The intramolecularly hydrogen-bonded peroxy acid molecule (or the dipolar form derived from it) has been recognized as the initial reactive species in the epoxidation reaction.[1]

Any reduction in the effective concentration of the cyclically bonded peroxy acid should thus reduce the rate of epoxidation. That epoxidation proceeds at a considerably slower rate in solvents capable of intermolecular association has already been clearly shown by Renolen and Ugelstad.[2]

Schwartz and Blumbergs[3] were the first to measure changes in the carbonyl frequency of *m*-chloroperoxybenzoic acid in methylene chloride containing acetonitrile, suggesting intermolecular association between peroxy acid and acetonitrile, but no further systematic attempts were made, to our knowledge, (1) to confirm or reject this type of association spectroscopically, or (2) to correlate the strength of the intermolecular hydrogen bonding with kinetic and activation parameters of epoxidation in these solvents. The infrared and kinetic studies to clarify this problem have been carried out and are discussed in this paper.

The lowering of the OH stretching frequencies and broadening of the corresponding OH stretching bands of *p*-nitroperoxybenzoic acid in ethyl acetate, diethyl ether, dioxane, tetrahydrofuran, and dimethylformamide, respectively, compared with intramolecularly

(1) A. Ažman, B. Borštnik, and B. Plesničar, *J. Org. Chem.*, **34**, 971 (1969), and references cited therein.
(2) P. Renolen and J. Ugelstad, *J. Chim. Phys.*, **57**, 634 (1960).
(3) N. N. Schwartz and J. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).

TABLE I

INFRARED DATA AND KINETIC PARAMETERS OF EPOXIDATION OF *trans*-STILBENE (4.0–4.3 × 10^{-2} *M*) WITH *p*-NITROPEROXYBENZOIC ACID (4.8–5.2 × 10^{-2} *M*) IN SOLVENTS WTH BASIC OXYGEN

Solvent	DC,[a] ϵ	DM,[a] μD	pK_b[b]	$\Delta\nu_{OH}$[c] ($\pm$8 cm^{-1})	k_2 × 10^4, l./mol sec 20°	25°	30°	E_a, kcal/mol	ΔS^*, eu, at 20°
Methylene chloride	8.9	1.5	...	0	55.5	...	118	13.3	−25.4
Ethyl acetate	6.2	1.85	19.1	33	2.72	4.41	7.09	16.9	−19.1
Diethyl ether	4.2	1.25	17.6	115	0.87	1.47	1.99[d]	18.1	−17.3
Dioxane	2.2	0.40	16.9	100	1.37	...	3.70	17.5	−18.3
Tetrahydrofuran	7.4	1.7	16.0	149	0.76	1.29	2.14	18.3	−17.0
Dimethylformamide	36.7	3.8	14.1	165	0.32	0.56	0.93	18.8	−16.7

[a] From "Handbook of Chemistry and Physics," 48th ed, The Chemical Rubber Co., Cleveland, Ohio, 1967. [b] From J. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co. Ltd., London, 1965. [c] The differences in frequencies between the intramolecular hydrogen-bonded OH absorption of *p*-nitroperoxybenzoic acid in methylene chloride (3285 cm^{-1}) and intermolecular hydrogen-bonded OH absorptions in solvents with basic oxygen. [d] Measured at 28°.

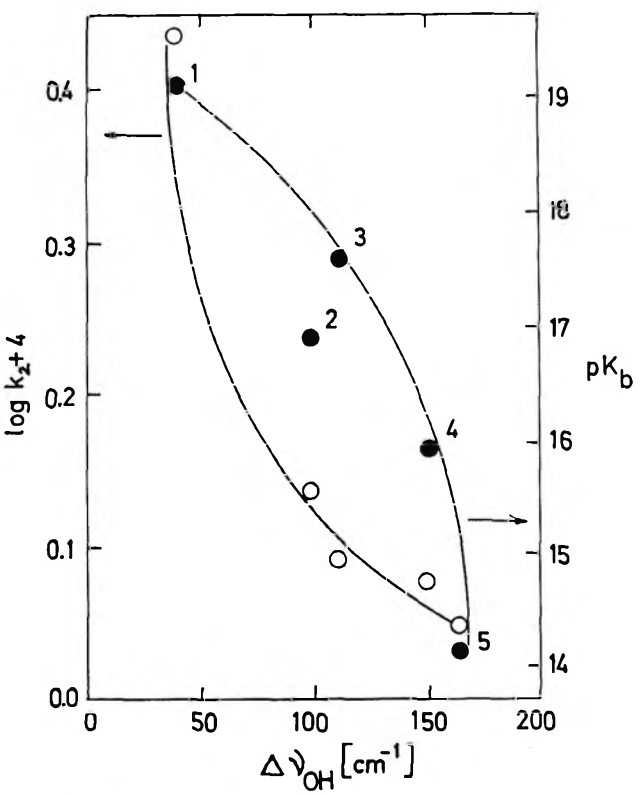
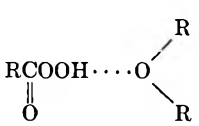


Figure 1.—Plots of logarithms of second-order rate constants of epoxidation of *trans*-stilbene with *p*-nitroperoxybenzoic acid in solvents with basic oxygen, and basicities (pK_b) of these solvents *vs.* $\Delta\nu_{OH}$, *i.e.*, the approximate strength of intermolecular hydrogen bonding between peroxy acid and a solvent: 1, ethyl acetate; 2, dioxane; 3, diethyl ether; 4, tetrahydrofuran; 5, dimethylformamide.

hydrogen-bonded OH in inert solvents, show that this peroxy acid exists in solvents with basic oxygen in the form of intermolecularly hydrogen-bonded adducts according to the following scheme.



The shift of the C=O stretching frequencies of peroxy acid to higher values in these solvents could also be taken as a support for the above-mentioned conclusion[4] ($\Delta\nu_{C=O}$ = 25 cm^{-1}).

(4) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960.

The kinetics of epoxidation of *trans*-stilbene with *p*-nitroperoxybenzoic acid in solvents under investigation was studied. The results of these measurements, along with the differences in frequencies between the intramolecular and intermolecular hydrogen-bonded OH absorptions of peroxy acid, which have been taken as a measure of an approximate strength of intermolecular association,[5] are collected in Table I.

Graphical presentation of the results in Figure 1 shows that the strength of intermolecular association between the peroxy acid molecule and a solvent increases with increasing basicity of solvents. It is also evident that the rate of epoxidation decreases in solvents which are capable of forming stronger intermolecular hydrogen bonds. The energies of activation of epoxidation are correspondingly higher in solvents which are more basic. There is a discrepancy between the expected and observed values only in the case of the solvent pair dioxane–diethyl ether. The activation energy of epoxidation, as well as $\Delta\nu_{OH}$, are higher in diethyl ether than in dioxane. It seems that diethyl ether behaves as more basic than dioxane in our system. Similar observations were made also by other workers.[6,7] An additional increase of the activation energy of epoxidation in diethyl ether in comparison with dioxane as a solvent, not expected solely on the basis of stronger intermolecular hydrogen bonding between peroxy acid and a solvent, could probably be attributed to the steric retardation in approaching the olefin molecule to the reactive center in the peroxy acid–solvent complex by methyl groups of diethyl ether.

The fact that the entropy of activation increases with increasing strength of intermolecular hydrogen bonding yields some further insight into the degree of orientation of the reactive species, *i.e.*, the greatest orientation of the peroxy acid–solvent complex in the case of solvents which form the strongest intermolecular hydrogen bonds with peroxy acid.

It is reasonable to assume on the basis of the above-mentioned results that the strength of the intermolecular association between peroxy acids and solvents with basic oxygen is one of the major factors influencing the kinetics of epoxidation in these solvents, although polarizabilities and steric requirements of solvents may also influence the rate of epoxidation in those cases where the differences in basicity of solvent pairs are small.

(5) M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965).
(6) C. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 2000 (1964).
(7) H. Normant, *Angew. Chem.*, **79**, 1029 (1967).

Experimental Section

p-Nitroperoxybenzoic acid was prepared and purified according to the procedure of Silbert, *et al.*[8] All the solvents used were Reagent grade commercial products and were dried and distilled before use. The purity of each was confirmed by vapor phase chromatography. *trans*-Stilbene, scintillation grade, was obtained from Fluka and used without further purification.

The infrared spectra were recorded at 20° on a Perkin-Elmer Model 521 infrared spectrophotometer using 0.05–0.10 mm cells (NaCl). Methylene chloride solutions of equimolar amounts of peroxy acid and a compound with basic oxygen were employed.

The kinetics of epoxidation was followed iodometrically according to Lynch and Pausacker.[9] Reactions were performed in 50-ml volumetric flasks. Samples (5 ml) were quenched in 2-*N* sulfuric acid cooled and degassed with small pinches of Dry Ice, an excess of potassium iodide was added (1 ml of 15% solution), and the liberated iodine was titrated with 0.05 *N* sodium thiosulfate without starch indicator. When ethyl acetate or diethyl ether were used as solvents, carbon tetrachloride was necessary to add to the titration mixture in order to obtain satisfactory end-points. Observed titres were corrected for the decomposition of peroxy acid in the corresponding solvent. Second-order rate constants were obtained from a linear least-squares program. Calculation of activation energies and entropies was performed by the usual method.[10] Errors (standard deviations) in second-order rate constants are ±2%, those in E_a are *ca.* ±0.5 kcal/mol, and those in $\Delta S^{\pm}$ are ±1.5 eu.

Registry No.—*trans*-Stilbene, 103-30-0; *p*-nitroperoxybenzoic acid, 943-39-5.

Acknowledgment.—The authors wish to thank Professor D. Hadži for his interest and encouragement. The financial support of this research by the Boris Kidrič Fund is also gratefully acknowledged.

(8) L. S. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, **27**, 1136 (1962).
(9) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).
(10) J. F. Bunnett, "Investigation of Rates and Mechanisms of Reaction," Part I, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1961.

pK_a Values of 4-Substituted 4′-Aminobenzanilides and 4′-Hydroxybenzanilides. A Search for Transmission of Electronic Effects through an Amide Linkage

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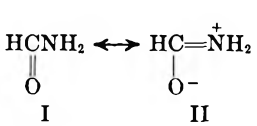
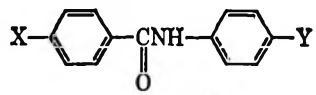
The planarity and restricted rotation of amide groups have been attributed to a dipolar resonance contributor II. Pauling[1] has estimated that I and



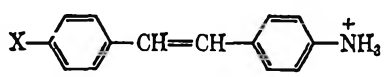
II contribute 60 and 40%, respectively, corresponding to 40% double-bond character for the C–N bond. One might expect, therefore, that two aromatic rings joined by an amide group would be conjugatively linked *via* the partial double bond. We show below that, on the contrary, there is no conjugative transmission in the ground states of compounds III.[2]

The degree of electronic interaction between the aromatic rings of IIIa and IIIb was estimated from

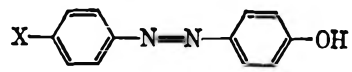


IIIa, Y = NH_3^+
b, Y = OH

the pK_a values presented in Table I. Since the pK_a values of the corresponding stilbenes (IV) and azobenzenes (V) are known,[3-5] it is possible to compare the amide group with the ethylene and azo functionalities.



IV



V

TABLE I
pK_a VALUES OF 4-SUBSTITUTED 4′-AMINOBENZANILIDES AND 4′-HYDROXYBENZANILIDES (IIIa AND IIIb)[a]

Y	X	pK_a
NH_3^+	OCH_3	4.62
NH_3^+	CH_3	4.52
NH_3^+	H	4.55
NH_3^+	Cl	4.54
NH_3^+	NO_2	4.48
OH	OCH_3	9.55
OH	CH_3	9.54
OH	H	9.54
OH	Cl	9.50
OH	NO_2	9.50

[a] Determined spectrophotometrically in 1.6% acetonitrile–water at 25.0°.

The Hammett ρ value for IIIa, calculated from the data in Table I, was found to be 0.09 ± 0.04 in 1.6% acetonitrile–water. This is considerably less than the ρ value for ionization of IV (0.422[3] and 0.684[4] in ethanol–water). The small ρ for IIIa cannot be attributed to an unusually small double-bond character of the amide C–N bond because the benzanilides show normal amide carbonyl bands in the infrared and because the presence of two phenyl rings should, if anything, enhance the contribution from the dipolar structure II. However, the possibility existed that resonance between the phenyl rings was unimportant in the conjugate base of IIIa because this would lead to a tetrapolar contributor. For this reason we determined the pK_a values of IIIb, a system

(1) L. Pauling, "Symposium on Protein Structure," A. Newberger, Ed., John Wiley & Sons, Inc., New York, N. Y., 1958, p 17.
(2) Conjugation in the excited state of benzanilides has been demonstrated by V. A. Izmail'skii and A. V. Malygina, *Zh. Obshch. Khim.*, **29**, 3935 (1959).
(3) H. Veschambre and A. Kergomard, *Bull. Soc. Chim. Fr.*, 336 (1966).
(4) M. Syz and H. Zollinger, *Helv. Chim. Acta*, **48**, 517 (1965).
(5) S. Yeh and H. H. Jaffé, *J. Amer. Chem. Soc.*, **91**, 3287 (1959).

TABLE II

MELTING POINTS AND ANALYSES OF 4-SUBSTITUTED 4'-HYDROXYBENZANILIDES

$XC_6H_4CONHC_6H_4OH$, X	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
OCH_3	230–232	69.12	5.39	5.76	68.96	5.44	5.71
CH_3	215–216	73.99	5.77	6.16	74.00	5.73	6.10
Cl	245–246	63.04	4.07	5.65	62.99	3.96	5.50
NO_2	265–266	60.46	3.90	10.85	60.44	3.77	10.77

in which resonance stabilization of the conjugate base (phenolate anion) results in dispersal of charge rather than in charge creation. The ρ value for ionization of IIIb in 1.6% acetonitrile–water was found to be 0.05 ± 0.02. This is 10 times less than the ρ for ionization of V (20% ethanol–water) and 6 times less than the ρ for ionization of substituted 4-hydroxystilbenes (1.6% acetonitrile–water).[6] Clearly, the amide linkage is a poor transmitter of electronic effects *despite the considerable double-bond character of the* C–N bond.[7]

In recent work, Johnson and coworkers[9] showed that Michael addition of ethanol to acrylanianilides and elimination of HBr from β-bromopropionanilides (ethanol, 55°) have a Hammett ρ of 1.77 and 1.74, respectively. The amide linkage, it was concluded, is an excellent transmitter of activation effects. On the basis of our results with the benzanilide systems, it would appear that the large ρ values for the addition and elimination reactions are due mainly to an efficient transmission of polar effects, and that there is little direct resonance interaction between the substituents and the reactive sites.

The reason for the lack of electronic transmission through the amide linkage is not clear. Perhaps the 60% reduction in double-bond character is sufficient to suppress completely any conjugative effects. Alternatively, the nature of the partial double bond of the amide group may be different from that of ethylenic and azo double bonds. The partial double bond of the amide could involve overlap between the unshared pair of electrons on the nitrogen and an empty carbon orbital in the 3 shell. This is consistent with an amide carbonyl bond length that is *shorter* than that of acetaldehyde.[10] Our results might also be related to Pauling's idea that polarization of the σ bond between the carbonyl carbon and the nitrogen effectively liberates a p orbital of carbon lying in the plane of the group, and permits a π bond to be formed with an unshared pair of electrons on the oxygen.[1]

Experimental Section

Compounds.—The general procedure used for the preparation of the substituted 4'-hydroxybenzanilides was as follows. A *para*-substituted benzoyl chloride (0.01 mol) was dissolved in 20 ml of pyridine that had been dried over Linde 4A Molecular Sieve. This solution was added dropwise to 20 ml of a pyridine solution of recrystallized *p*-hydroxyaniline (0.01 mol). The reaction mixture was then boiled under reflux for 12 hr, after which the pyridine was removed with the aid of a rotary evaporator. The residue was crystallized from ethanol–water and sublimed. The properties of the products are given in Table II.

Substituted 4'-aminobenzanilides were prepared by the method of Izmail'skii and Malygina.[2]

pK_a Determinations.—The pK_a values of the benzanilides and stilbenes were determined spectrophotometrically by the method of Albert and Serjeant.[11]

Registry No.—IIIa (X = OCH_3), 23600-43-3; IIIa (X = CH_3), 23600-44-4; IIIa (X = H), 17625-83-1; IIIa, (X = Cl), 23600-46-6; IIIa (X = NO_2), 6409-40-1; IIIb (X = OCH_3), 23600-48-8; IIIb (X = CH_3), 23646-69-7; IIIb (X = H), 15457-50-8; IIIb (X = Cl), 19207-92-2; IIIb (X = NO_2), 13160-56-0.

Acknowledgment.—This work was supported in part by a grant from the National Science Foundation.

(6) The ρ was determined from a two-point Hammett plot.

(7) The ionization of *para*-substituted N-methylbenzhydroxamic acids has a ρ of 0.86 in 80% Methyl Cellusolve–water.[8] This ρ is less than that for the ionization of benzoic acid in water, and it suggests that there may be also little direct resonance interaction through the carbonyl carbon–nitrogen bond of the hydroxamic acids. Morever, the pK_a values correlate with σ rather than with σ^-.

(8) O. Exner and W. Simon, *Collect. Czech. Chem. Commun.*, **30**, 4078 (1965).

(9) H. W. Johnson, E. Ngo, R. C. Stafford, and Y. Iwata, the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Organic Abstract No. 31.

(10) H. A. Bent, *Chem. Rev.*, **68**, 587 (1969).

(11) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co. Ltd., London, 1962, p 69.

Stereochemistry of α-Phenethyl Radical Dimerization[1]

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It has been reported[3] that the reduction of α-bromoethylbenzene and α-chloroethylbenzene by chromous sulfate produces 85–90% *meso*-2,3-diphenylbutane and 10–15% the *dl* forms, the disparity being attributed to conformational effects. If correct, this observation would connote a mechanism of final product formation other than simple dimerization of free radicals, because there is abundant qualitative and semiquantitative evidence[4] based on yields in other free-radical situations

(1) Work was supported by the Atomic Energy Commission.

(2) Summer Student Training Program, Argonne National Laboratory, 1969, supported in part by the National Science Foundation.

(3) C. E. Castro and W. C. Kray, Jr., *J. Amer. Chem. Soc.*, **85**, 2768 (1963).

(4) Comparable yields of *meso*- and *dl*-2,3-diphenylbutane have been reported in (a) the reaction of α-chloroethylbenzene with magnesium and moist ether [E. Ott, *Chem. Ber.*, **61**, 2124 (1928)]; (b) α-bromoethylbenzene with sodium [K. T. Serijan and P. H. Wise, *J. Amer. Chem. Soc.*, **74**, 365 (1952)]; (c) α-bromoethylbenzene with magnesium and cupric chloride [J. B. Conant and A. H. Blatt, *ibid.*, **50**, 551 (1928)]; (d) coupling of Grignard reagent [W. T. Somerville and P. E. Spoerri, *ibid.*, **74**, 3803 (1952)]; (e) decomposition of diacetyl peroxide in ethylbenzene [M. S. Kharasch, H. McBay, and W. H. Urry, *J. Org. Chem.*, **10**, 401 (1945)]; (f) decomposition of di-*t*-butyl peroxide in ethylbenzene [E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, **1951**, 131]; (g) decomposition of benzoyl peroxide in ethylbenzene [R. L. Dannley and B. Zaremsky, *J. Amer. Chem. Soc.*, **77**, 1588 (1955)]. In one instance, the reaction of hydrotropoyl chloride with sodium peroxide, the equality of yields was established by careful ir analysis [F. D. Greene, *ibid.*, **77**, 4869 (1965)].

to show that α-phenylethyl radicals dimerize in the two modes nearly equally. It seemed desirable in connection with concurrent studies on reduction by the hydrated electron to recheck the chromous sulfate reduction and, also, with the more refined analytical procedures now available, to test more rigorously for the presence or absence of measurable stereo discrimination in some conventional free-radical dimerizations.

The conventional reactions giving rise to 2,3-diphenylbutane mixtures, and believed to occur by dimerization of α-phenethyl radicals, were (1) decomposition of di-*t*-butyl peroxide in ethylbenzene at 135°;[4f] (2) decomposition of benzoyl peroxide in ethylbenzene at 100°;[4g] (3) reaction of ethylbenzene with aqueous potassium persulfate at 80°;[5] (4) reaction of α-bromoethylbenzene with iron powder in water suspension;[6] (5) reaction of α-bromoethylbenzene vapor with a silver mirror film at 25°;[7] (6) benzophenone-sensitized photolysis of ethylbenzene at three different temperatures, −25, −73, and −110°.[8] The choices were influenced by the thought that reactions at the lowest possible temperature, or on surfaces, would be most likely to reveal any small measure of steric control. No attempt was made to maximize yields and care was taken to avoid fractional separation of isomers prior to a determination of the *meso*/*dl* ratio by gas chromatography. All of the results (*cf.* Table I) agreed, within

TABLE I
ISOMER RATIOS IN REACTIONS FORMING 2,3-DIPHENYLBUTANE

Reaction no.	Reactants	Temp, °C	Time, hr	*meso*/*dl* ratio
1	Ethylbenzene, di-*t*-butylperoxide	135	3	1.08
2	Ethylbenzene, benzoyl peroxide	100	2	1.02
3	Ethylbenzene, aq $K_2S_2O_8$	100	4	1.01
4	α-Bromoethylbenzene, Fe, aq suspn	80	3.5	1.03
5	α-Bromoethylbenzene (vapor), Ag mirror	25	45	0.98
6a	0.12 *M* ethylbenzene, 0.02 *M* benzophenone in benzene, 3600-Å irradn	25	0.5 1.5 3.0	1.00 1.04 1.03
6b	0.02 *M* benzophenone in ethylbenzene	−25 −73 −110	1.0 1.0 1.0	1.02 0.98 1.03
7	α-Bromoethylbenzene, aq $CrSO_4$	25 0	0.2 0.5	1.05 1.06

the limits of experimental error, with the assignment of equal probability to *meso* and *dl* product formation. The overall average, 1.020 ± 0.020 (average deviation), deviated slightly in favor of the *meso* form but the direction and magnitude of the deviation is about what might be expected from slight tailing of the *dl* peak into the region of the *meso* peak.

Likewise the product ratio from the chromous sulfate reduction of α-bromoethylbenzene (*cf.* Table I, reaction 7) showed no clearly significant departure from random orientation of the combining radicals. It follows that yields of isolated crystalline *meso* isomer in excess of 50% of theoretical cannot be reconciled with these measurements and hence that the reported[3] actual yields, 56 and 81% from α-bromo- and α-chlorobenzene, respectively, are too imprecise to be mechanistically significant. The new measurements are consistent with, but of course do not uniquely validate, the currently accepted[9] free-radical interpretation of halide reduction by chromous salts.

Experimental Section

Gas chromatographic analyses were performed on 7-m QF-1 columns operated at 125–150° or, in a few instances, on an 8-m OV-101 column at 195°. The latter provided a somewhat cleaner separation of *dl*- and *meso*-2,3-diphenylbutane, eluting in the order named, but the higher operating temperature was a disadvantage. Isomer ratios were based on peak areas as determined by disk integration.

Reactions 1–4, as enumerated above, were conducted on a gram scale and under a nitrogen atmosphere but otherwise under reaction conditions as described in the literature. Upon termination of the reactions in homogeneous mixtures, as in reactions 1, 2, and 6, samples were injected directly into the chromatograph. In other cases, namely reactions 3, 4, 5, and 7, ether extracts were made and samples thereof were injected. Reaction 5 was conducted by introducing a few milligrams of liquid α-bromoethylbenzene into a side arm on an evacuated silvered flask which, after sealing, was stored in the dark at room temperature for 2 days. In the photolysis experiments, solutions of benzophenone (0.02 *M*) in ethylbenzene, contained in Pyrex tubes and purged with nitrogen gas, were suspended in an alcohol-filled, windowed dewar flask and exposed for 60 min to 3600-Å illumination from a General Electric H 100 BL lamp. Some photolysis experiments were performed, at room temperature, with benzene as solvent.

The chromous sulfate reagent was prepared for us[10] as described in an earlier paper by Castro[11] and was diluted to the required 0.45 *N* immediately before use. The reduction of α-bromoethylbenzene, 1.4 g in 25 ml of dimethylformamide, was done, first at room temperature, by addition to 25 ml of the reagent, vigorously stirred in a nitrogen-purged system. There was an immediate color change to dark green and noticeable warming of the mixture. After about 10 min, the separated product became semicrystalline and no further change was apparent on continued stirring for 2 hr. Extraction with three 20-ml portions of ether, followed by backwashing of the combined ether extracts with water and evaporation of most of the ether (after removal of a sample for chromatographic analysis), furnished 0.26 g (36%) of crystalline *meso*-2,3-diphenylbutane and 0.50 g of mother liquor. In a similar experiment, in which the reactants were cooled to ice-bath temperature before mixing, the initial color change occurred in a period of about 1 min, semicrystalline product appeared very quickly, and no further change was seen on continued stirring for 5 hr. The ether extract upon concentration deposited 0.19 g of *meso* isomer and the mother liquor (0.54 g) assayed 34% *dl* and 3% *meso*.

Registry No.—*meso*-2,3-Diphenylbutane, 3755-79-1; *dl*-2,3-diphenylbutane, 4656-85-3.

(5) C. Moritz and R. Wolffenstein, *Chem. Ber.*, **32**, 432 (1899).
(6) K. Sisido and H. Plozaki, *J. Amer. Chem. Soc.*, **70**, 778 (1948).
(7) This particular application of silver to effect dimerization appears not to have been previously mentioned but the prototype is well known.
(8) E. Paternò and G. Chieffi, *Gazz. Chim. Ital.*, **39** [II], 415; *Chem. Abstr.*, **5**, 682 (1911).
(9) The subject of mechanism in chromium(II) reductions has been reviewed by J. R. Hanson and E. Premuzic, *Angew. Chem. Int. Ed. Engl.*, **7**, 247 (1969).
(10) We are indebted to J. C. Sullivan and D. L. Toppen for a supply of the reagent.
(11) C. E. Castro, *J. Amer. Chem. Soc.*, **83**, 3262 (1961).

Long-Range Splitting in the Nuclear Magnetic Resonance Spectrum of 1,4-Dihydrobenzoic Acid

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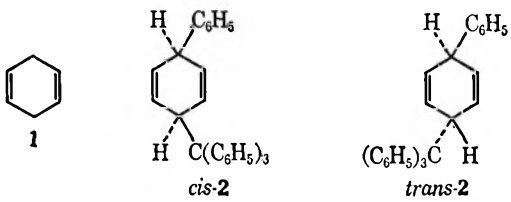
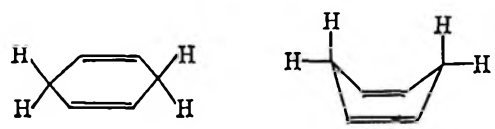
Previous examples of homoallylic proton–proton coupling[1] (with a symmetrically disposed π bond) indicate that this long-range coupling is generally very small[1-5]—such coupling constants usually do not exceed 3 Hz.[6] However, the 1,4-cyclohexadiene system has been reported to give an unusually large homoallylic coupling constant: 1,4-cyclohexadiene (**1**) has *cis* and *trans* coupling constants of 9.63 and 8.04 Hz, respectively,[7] and the isomeric 1-phenyl-4-trityl-1,4-cyclohexadienes (**2**) have *cis* and *trans* coupling constants of 11 and 7.5 Hz, respectively.[8]



1 *cis*-**2** *trans*-**2**

The large homoallylic coupling in 1,4-cyclohexadienes has allowed some workers to attach special significance to J_{cis}/J_{trans} ratios thus obtained. The small J_{cis}/J_{trans} ratio for **1** (*viz.*, 1.2) prompted Garbisch[7] to postulate a planar, or nearly so, conformation for 1,4-cyclohexadiene (**3**) rather than a highly puckered, or boat, conformation (**4**). Implicit in his discussion

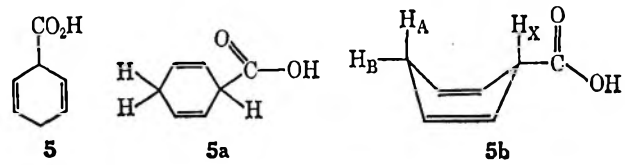


3 **4**

was the assumption that for the planar conformation (**3**), $J_{cis} = J_{trans}$.[9]

Atkinson and Perkins, who investigated the nmr of **2**, believed that for the planar conformation (**3**) J_{cis} should be less than J_{trans}, that $J_{cis} = J_{trans}$ only when the ring is somewhat puckered, and that 1,4-cyclohexadiene is therefore *not* planar. For **2**, they argued, the bulky substituents exaggerated the puckering to such an extent that now J_{cis} was considerably greater than J_{trans} ($J_{cis}/J_{trans} = 1.47$).

We report here our nmr studies of 1,4-dihydrobenzoic acid (**5**), a compound whose sterical requirements are somewhat different from those of **1** or **2**. Models indicate that in planar **5** steric interaction occurs be-

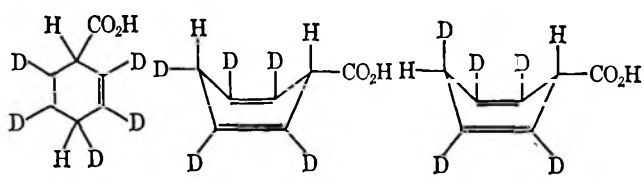


5 **5a** **5b**

tween the carboxylate group and the olefinic π bonds (see **5a**), and that a puckered conformation (**5b**) would be preferred with the carboxylate group in a pseudo-equatorial position. The puckering in **5**, however, should not be as severe as in **2**. Thus, **5** should represent a case between **1** and **2**, unless **1** is highly puckered also.

The 60-MHz nmr spectrum of **5** exhibited a singlet at δ 11.71 (acid proton), a singlet at δ 5.80 (olefinic), a triplet at δ 3.71 with $J = 8.6$ Hz (methine), and a doublet at δ 2.53 with $J = 8.6$ (allylic). A first-order analysis of the spectrum, therefore, indicated that homoallylic coupling between the methine and the methylene protons existed to give a simple AX_2 system. The latter three signals, however, included perturbations which could arise from olefinic–aliphatic coupling and/or an actual ABX system.[10] The 100-MHz spectrum, with proton–proton decoupling,[11] indicated that most of the perturbations were due to olefinic–aliphatic coupling: the uncoupled olefinic signal appeared as a triplet (with a separation of 2 Hz) but simplified when either the methine or the methylene signals were irradiated, and irradiation of the olefinic signal simplified the methine and the methylene signals.

The nmr spectrum of **5** would also be consistent with a deceptively simple ABX system where both $\nu_0\delta_{AB}$ and $^1/_2(J_{AX} - J_{BX})$ are small compared with J_{AB}, and with the apparent coupling constant J_{app} being an average of J_{AX} and J_{BX}[12] (see **5b** where J_{AX} is J_{cis} and J_{BX} is J_{trans}). To explore the possibility of such a system, a sample of 2,3,4,5,6-pentadeuterio-1,4-dihydrobenzoic



6 *cis*-**6** *trans*-**6**

acid (**6**) was prepared (see Experimental Section). The sample of **6** was undoubtedly a mixture of *cis*- and

(1) J. T. Pinhey and S. Sternhell, *Tetrahedron Lett.*, 275 (1963).
(2) J. H. Richards and W. F. Beach, *J. Org. Chem.*, **26**, 623 (1961).
(3) W. F. Beach and J. H. Richards, *ibid.*, **26**, 3011 (1961).
(4) R. R. Frazer, *Can. J. Chem.*, **38**, 549 (1960).
(5) S. Gronowitz, B. Gestblom, and R. A. Hoffman, *Acta Chem. Scand.*, **15**, 1201 (1961).
(6) For an excellent review, see S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).
(7) E. W. Garbisch, Jr. and M. G. Griffith, *J. Amer. Chem. Soc.*, **90**, 3590 (1968).
(8) D. J. Atkinson and M. J. Perkins, *Tetrahedron Lett.*, 2335 (1969).
(9) M. Karplus, *J. Chem. Phys.*, **33**, 1842 (1960).
(10) In 9,10-dihydroanthracene systems, the two allylic protons can have a chemical shift up to 0.3 ppm and can have a coupling constant of 18 Hz: D. Nicholls and M. Szwarc, *J. Amer. Chem. Soc.*, **88**, 5757 (1966); R. G. Harvey, L. Arzadon, J. Grant, and K. Urberg, *ibid.*, **91**, 4535 (1969).
(11) We wish to thank D. H. Gibson and A. Shultz, University of Colorado, Boulder, Colo., for recording the 100-MHz spectra and for the irradiation experiments.
(12) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, New York, N. Y., 1965, p 363; R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961). Since J_{AB} should be about 18 Hz,[10] $\nu_0\delta_{AB}$ and $^1/_2(J_{AX} - J_{BX})$ could be a few hertz or less.

trans-dihydro compound[7,13-15] (*cis*-**6** and *trans*-**6**). If J_{cis} were significantly different from J_{trans}, then in the nmr spectrum of **6** each isomer should have two doublets distinguishable from those of the other isomer. However, the nmr spectrum of **6** exhibited (along with an acid proton at δ 12.05) only two sharp doublets centered at δ 3.73 and 2.58 with J = 8.3 Hz.[16] Thus, J_{cis} and J_{trans} were not significantly different.

The coupling constants for **5** and for **6** were slightly different (0.3 Hz). This observation has the following implications. In our sample of **6**, one isomer (either *cis* or *trans*) predominated whose coupling constant was 8.3 Hz. The other isomer, in order to average out J_{app} in **5** to be 8.6 Hz in an ABX system, must have J = 8.9 Hz. Thus, the J_{cis}/J_{trans} ratio (either 8.3/8.9 = 0.93 or 8.9/8.3 = 1.07) would be very close to unity.

If the puckering in **5** were intermediate between that in **1** and **2**, one would expect the J_{cis}/J_{trans} ratio for **5** to be between that of **1** and **2**. However, the ratio for **5** lies outside this range and is less than that for **1**. It is difficult to believe that **5** is *less* puckered than **1**. Instead, it is to be concluded that the J_{cis}/J_{trans} ratio is only a rough approximation of the degree of puckering, and that **1** and **5** are puckered to about the same extent. Since **5** would be expected to be puckered (*vide supra*), it would seem that 1,4-cyclohexadiene (**1**) is definitely in a boat conformation and that a single moderately sized substituent can be fitted into this conformation comfortably in the pseudo-equatorial position.

Experimental Section

Melting points were determined by a Thomas-Hoover melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer and a Varian HA-100 spectrometer, using tetramethylsilane as the internal standard. Ultraviolet spectra were recorded on a Beckman DB spectrophotometer.

1,4-Dihydrobenzoic Acid (5).—This compound was prepared from benzoic acid by the procedure of Kuehne and Lambert[13] and was transparent in the region of 240–270 mμ, indicating the absence of the 1,3-cyclohexadiene chromophore.

Benzoic Acid-d_5.—Reaction of bromobenzene-d_5 (Stohler Isotope Chemicals, Azusa, Calif.) with magnesium and subsequent carbonation with Dry Ice[17] gave benzoic acid-d_5 in a 50% yield, mp (H_2O) 119–121°. An nmr spectrum of the product exhibited no signals in the aromatic region.

2,3,4,5,6-Pentadeuterio-1,4-dihydrobenzoic Acid (6).—Birch reduction of benzoic acid-d_5 in the usual manner[13] gave an 82% yield of **6**, bp 77–79° (0.4 mm).

Registry No.—**5**, 4794-04-1.

Acknowledgment.—Acknowledgment is made to the Research Corporation (Frederick Gardner Cottrell Grant-in-Aid), to the Robert A. Welch Foundation, Grant No. B-325, and to North Texas State University for a Faculty Research Grant for support of this work.

(13) M. E. Kuehne and B. F. Lambert, *Org. Syn.*, **43**, 22 (1963).
(14) G. W. Brown and F. Sondheimer, *J. Amer. Chem. Soc.*, **89**, 7116 (1967).
(15) R. G. Harvey, L. Arzadon, J. Grant, and K. Urberg, *ibid.*, **91**, 4535 (1969).
(16) Owing to the small extent of aliphatic–olefinic coupling in **5**, D–H coupling in **6** was negligible and deuterium decoupling was not necessary.
(17) H. Gilman, N. B. St. John, and F. Schulze, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 425. Our procedure is different from that of Gilman in that the Grignard reaction mixture was poured over Dry Ice instead of bubbling in gaseous carbon dioxide.

Electronic and Nuclear Magnetic Resonance Spectra of Dithizone

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Several metal complexes of dithizone (1,5-diphenylthiocarbazone) are photochromic when irradiated with visible light.[1] During a study of this photochromic system,[2] we became interested in the electronic spectra and photochromism of dithizone itself.

When dissolved in methylene chloride, dithizone forms an intense green solution having the spectrum shown by the solid line in Figure 1. Intense irradiation of the green solution with visible light, in *dry*, nonpolar solvents, produces a red, metastable form (dashed line in Figure 1) which returns very rapidly to the original green.[3] The orange, nonphotochromic dithizonate anion produced in alkaline solution is shown by the dotted line in Figure 1.

It is unusual for a neutral molecule of this size to possess the intense, low-energy absorption (molar absorptivity $\cong$ 37,000 at 6100 Å) shown by the long-wavelength band of the green form. No comparable band exists for the oxygen analog of dithizone (diphenylcarbazone) which is orange in neutral solution because of a weak n $\rightarrow$ π^* transition appearing as a shoulder on intense ultraviolet $\pi \rightarrow \pi^*$ transitions.

The relative intensities and λ_{max} values for the two visible bands in the dithizone spectrum depend upon the solvent, and some workers[4] have interpreted these changes to indicate that the two bands originate from a thiol–thione tautomeric system. Although we have observed such solvent effects, we have been unable to interpret them rigorously, since they appear to be complicated by acid–base equilibria, trace metal effects, and even oxidative decomposition of the dithizone.

We could not obtain the nmr spectrum of dithizone itself because of poor solubility, but we have obtained the spectrum of an alkylated derivative [1,5-di(*o*-ethylphenyl)thiocarbazone] in $CDCl_3$. The chemical shifts (τ values referred to TMS, Varian A-60) were −2.03 (1.6 protons), 1.9 and 2.67 (8 aromatic), 7.0 (4 methylene), and 8.6 (6 methyl). The signal at τ −2.03 showed no evidence of splitting over the temperature range +50 to −45° in $CHCl_3$ solution (in fact, the peak became somewhat narrower at lower temperatures) and disappeared upon addition of CH_3OD.

We feel that these nmr results favor a single (equivalent proton) structure instead of rapid exchange between a form containing S–H and a form containing N–H. For the latter case we would expect splitting

(1) L. S. Meriwether, E. C. Breitner, and C. L. Sloan, *J. Amer. Chem. Soc.*, **87**, 4441 (1965).
(2) R. A. Coleman, W. H. Foster, Jr., J. Kazan, and M. Mason, Final report, "Synthesis of Chromotropic Colorants," Feb 1966, U. S. Army Natick Laboratories, Natick, Mass., Contract No. DA19-129-AMC-269(N), issued as Technical Report 66-0-CM, Series TS-138, AD630908.
(3) The photochromism of dithizone was previously reported by Meriwether, *et al.*[1]
(4) P. S. Pel'kis and R. G. Dubenko, *Zh. Obshch. Khim.*, **29**, 194 (1959).

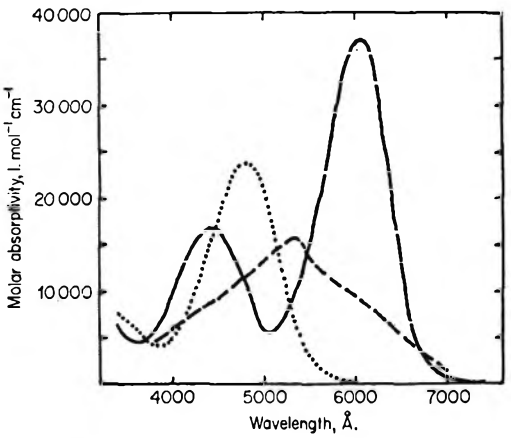
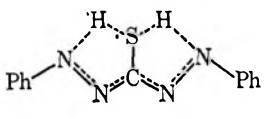


Figure 1.—Electronic spectra of three forms of diphenylthiocarbazone: ———, methylene chloride at room temperature; ·····, alkaline methylene chloride–methanol at room temperature (~0.005 *N* NaOH in 95% (vol) methylene chloride–5% methanol); – – – –, hexane at ~1°, while irradiated with the full intensity of the near-infrared tungsten lamp in the Cary 14.

(or at least broadening) of the τ −2.03 peak at low temperature instead of the slight narrowing which was observed.

We propose structure **1** to represent the green form existing in neutral solutions of dithizone.



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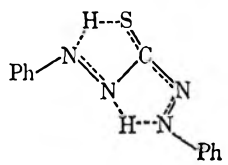

2

Structure **2**, which can be obtained by isomerization about a carbon–nitrogen double bond, may be responsible for the red, metastable form. The nmr spectrum of this form cannot be studied, since the incident light beam is completely absorbed at the surface of the concentrated solutions required for nmr. Consequently only a small fraction of the molecules is converted to the metastable form.

The exact explanation for the intensity of the long-wavelength peak in the spectrum of the green form is still lacking, but it appears unlikely that a simple thiol–thione tautomeric system can account for the spectrum.

Registry No.—Dithizone, 60-10-6.

Acknowledgment.—This work was supported in part by the U. S. Army Natick Laboratories, Natick, Mass.

Reaction of Diazomethane with Some α,β-Unsaturated Acetals and Aldehydes

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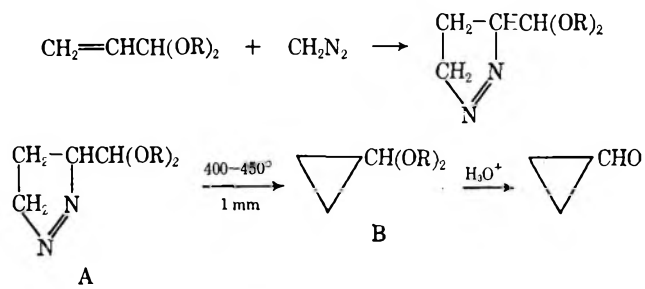
A fairly recent report[1] has described an improved method of synthesis of cyclopropanecarboxaldehyde by ceric nitrate oxidation of cyclopropylcarbinol. We wish to report a new synthesis of this aldehyde which represents at least a more economical method, since cyclopropylcarbinol is a relatively expensive starting material. This procedure involves a three-step sequence with various acrolein acetals as starting materials—each step being accomplished in good to excellent yields. Acrolein acetals, including the cyclic 2-vinyl-1,3-dioxolanes and 2-vinyl-1,3-dioxanes, can be obtained commerically or may be conveniently prepared from acrolein.[2] Reaction of diazomethane with the unsaturated acetal forms a 1-pyrazoline. This can be readily pyrolyzed to the corresponding acetal of cyclopropane carboxaldehyde, which is then hydrolyzed to the aldehyde. Overall yields for the three steps ranged as high as 50%. Table I lists yields, physical



constants, and elementary analytical data for compounds of types A and B as prepared from different acrolein acetals.

The pyrazolines obtained from all of the acrolein acetals used were of the indicated Δ^1 structure, as evidenced by the lack of an NH absorption band near 3400 cm^{-1} and the presence of an N=N absorption at 1540 cm^{-1} in the infrared spectra. The direction of addition of diazomethane to the double bond is assumed to be that demonstrated for alkene linkages having other adjacent electron-withdrawing groups.[3]

Vapor phase pyrolysis of the pyrazolines, following the method used by McGreer,[4] gave yields of 73–96%. These pyrazolines proved to be relatively more heat stable, and higher temperatures (400–450°) and lower pressure (1 mm) were necessary than for the conjugated pyrazolines pyrolyzed in McGreer's work. A number of unsuccessful attempts were made to photolyze these pyrazolines, using a 450-W Hanovia lamp.

The most difficult step for which to develop good yields proved to be the final hydrolysis. Use of inorganic acid solutions resulted in very poor yields. The best method developed during our study involved the use of a minimum amount of trichloroacetic acid to effect the water solution. With the cyclic acetals, yields of cyclopropanecarboxaldehyde were much better than with the diethyl acetal, owing to the difficulty of complete separation of ethanol from the aldehyde in the latter case.

An investigation was also made of the reaction of diazomethane with acrolein itself, in the hope of realizing a two-step synthesis of cyclopropanecarboxaldehyde. Although a rapid reaction occurred, it proved to be impossible to isolate the simple addition

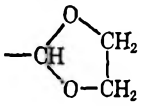
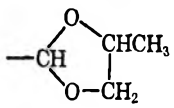
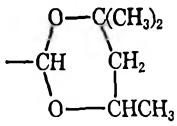
(1) L. B. Young and W. S. Trahanovsky, *J. Org. Chem.*, **32**, 2349 (1967).

(2) R. F. Fischer and C. W. Smith, *ibid.*, **25**, 319 (1960).

(3) R. Huisgen, R. Grashey and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, London, 1964, Chapter 11.

(4) D. E. McGreer, W. Wai, and G. Carmichael, *Can. J. Chem.*, **38**, 2410 (1960).

TABLE I

Compd	Acetal group	Compd type[a]	Yield, %	Bp, °C (mm)	$n^{25}D$	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1		a	80	76–77 (1)	1.4774	$C_6H_{10}N_2O_2$	50.69	7.09	50.47	6.91
2		a	68–75	85–86 (1)	1.4677	$C_7H_{12}N_2O_2$	53.83	7.74	54.00	7.90
		b	73–79	78–79 (60)	1.4326	$C_7H_{12}O_2$	65.58	9.45	65.39	9.59
3		a	77	79–81 (0.3)	1.4632	$C_{10}H_{18}N_2O_2$	60.58	9.15	60.59	9.24
		b	82–96	85–86 (10)	1.4436	$C_{10}H_{18}O_2$	70.56	10.66	70.69	10.52
4	$-CH(OC_2H_5)_2$	a	58	68–69 (1)	1.4435	$C_8H_{16}N_2O_2$	55.80	9.36	55.64	9.46
		b	82	47–48 (18)	1.4090	$C_8H_{16}O_2$	66.63	11.18	66.41	10.98

[a] a, 1-Pyrazolinecarboxaldehyde acetals; b, cyclopropanecarboxaldehyde acetals.

product, pyrazoline-3-carboxaldehyde, in even a fair yield. A competing reaction of diazomethane with the aldehyde group resulted in a second product, 3-acetyl-2-pyrazoline. Thus mixtures of the desired aldehyde and the ketone were formed when a 1:1 ratio of diazomethane and acrolein was used. With a 2:1 ratio of diazomethane to acrolein, good yields of 3-acetylpyrazoline were obtained. This compound was identical with that formed by addition of diazomethane to methyl vinyl ketone and is apparently a mixture of the tautomeric Δ^1- and Δ^2-pyrazolines. An infrared absorption band at 1550 cm^{-1}, ascribed to N=N stretching, indicated that some Δ^1-pyrazoline structure was present, although only conjugated carbonyl was indicated by absorption at 1670 cm^{-1}. No previous report of this reaction of acrolein was found, but the corresponding reaction of cinnamaldehyde has been reported[5] to give 4-phenyl-2-pyrazoline-3-carboxaldehyde. When we repeated this reaction with a 1:1 ratio of reactants, an unstable mixture was obtained. Using an excess of diazomethane, 3-acetyl-4-phenylpyrazoline could be isolated in fairly good yield. Again as with the acrolein product, the infrared spectrum indicated that both 1-pyrazoline and 2-pyrazoline structures were present. Methacrolein and diazomethane reacted in the same manner and, with an excess of diazomethane, 3-acetyl-3-methyl-1-pyrazoline was obtained.

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained with a Beckman Model IR-5.

Acrolein Acetals.—Acrolein diethyl acetal was prepared according to the method of VanAllan.[6] Various 2-vinyl-1,3-dioxolanes or 2-vinyl-1,3-dioxanes were prepared from acrolein and the appropriate glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid as described by Fischer and Smith:[2] **2-vinyl-1,3-dioxolane**, bp 109–113° (690 mm), $n^{25}D$ 1.4281; **2-vinyl-4-methyl-1,3-dioxolane**, bp 50–51° (50 mm), $n^{25}D$ 1.4218; **2-vinyl-4,4,6-trimethyl-1,3-dioxane**, bp 88–90° (53 mm), $n^{25}D$ 1.4359.

Reaction of Diazomethane with Acrolein Acetals.—An ether solution of diazomethane, prepared by potassium hydroxide hydrolysis of *p*-tolylsulfonylmethylnitrosoamide ("Diazald," Aldrich Chemical Co.)[7] was distilled directly into a stirred and externally cooled solution of the acrolein acetal in ether. After addition was complete, stirring was continued for 1 hr and the solution was then poured into precooled pressure bottles which were sealed and kept at room temperature for 1–3 days. Removal of ether and vacuum distillation gave the product pyrazolines (see Table I, compound type **a**). Prepared were 2-(3-pyrazolinyl)-1,3-dioxolane (**1a**); 2-(3-pyrazolinyl)-4-methyl-1,3-dioxolane (**2a**); 2-(3-pyrazolinyl)-4,4,6-trimethyl-1,3-dioxane (**3a**); and pyrazoline-3-carboxaldehyde diethyl acetal (**4a**).

Pyrolysis of the Pyrazoline-3-carboxaldehyde Acetals (a).—A preheated sample of the pyrazolinyl acetal was placed in a dropping funnel equipped with a pressure-equalizing tube and attached to the top of a glass column packed to a distance of 20 cm with pieces of broken Pyrex glass tubing. A filter flask chilled externally with ice was attached to the bottom of the column and a tube from the side arm led to another filter flask chilled with Dry Ice. The column was heated to a temperature of 400–450° by a furnace, and the system was maintained at a pressure of 1 mm during dropwise addition of the pyrazoline. Products were directly distilled under reduced pressure. (See Table I, compound type **b**.)

Hydrolysis of the Cyclopropanecarboxaldehyde Acetals.—To 0.02 mol of the acetal was added 2–5 ml of 1 *N* trichloroacetic acid, sufficient to form a homogeneous solution upon stirring. Some warming helped with the higher molecular weight acetals. The mixture was usually stirred for 3–5 hr. It was then dried ($MgSO_4$) and distilled, or directly distilled to give a two-phase mixture of cyclopropanecarboxaldehyde and water, dried ($MgSO_4$), and redistilled. Yields ranged from 60 (for **4b**) to 96% (for **2b**), bp 92–95° (690 mm), $n^{25}D$ 1.4280 [lit.[8] bp 97–100° (740 mm), $n^{20}D$ 1.4302].

Reaction of Excess Diazomethane with α,β-Unsaturated Aldehydes. A. With Acrolein.—An ether–diazomethane mixture, prepared as previously described from 0.3 mol of Diazald, was distilled into an ice-cooled, stirred, 10% solution of 0.1 mol of acrolein in ether. Some amorphous orange solid, which was apparently polymeric, precipitated during the addition. The mixture was sealed in a pressure bottle and kept in a refrigerator overnight. The solution was decanted from the gummy solid and distillation gave a yellow liquid, bp 60° (0.5 mm), which quickly crystallized to an orange solid. Three recrystallizations from 10:1 ether–petroleum ether (bp 30–60°) resulted in light yellow crystals of 3-acetyl-2-pyrazoline: mp 60–62°; ir (CCl_4), 3400 (NH), 1670 (conjugated C=O), 1550 (N=N), and 1410 cm^{-1}. This compound was identical in melting point and ir spectrum with the product of addition of diazomethane to methyl vinyl ketone, and a mixture melting point determination showed no depression.

B. With Methacrolein.—A procedure similar to that above yielded 67% of colorless, liquid 3-acetyl-3-methyl-1-pyrazoline: bp 44–45° (0.2 mm); $n^{25}D$ 1.4625; ir (neat) 1720 (C=O), 1545 (N=N), and 1447 cm^{-1}.

(5) K. Kratzl and E. Wittman, *Monatsh. Chem.*, **85**, 7 (1954).

(6) J. A. VanAllan, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 21.

(7) T. J. deBoer and H. J. Backer, ref 6, p 250.

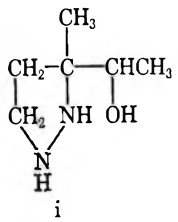
(8) H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **83**, 2016 (1961).

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99. Found: C, 56.92; H, 8.22.

The phenylhydrazone melted at 119–120°. The semicarbazone did not have a sharp melting point, deforming and carmellizing at 230–240°.

Anal. Calcd for $C_6H_{11}N_5O$: C, 42.60; H, 6.54. Found: C, 42.49; H, 6.49.

A sample of the ketone in ethanol was hydrogenated with Raney nickel catalyst at 1000 psi and room temperature. Distillation gave a very viscous, colorless liquid assumed to be i, bp 89° (0.5 mm), $n^{29}D$ 1.4891.



i

Anal. Calcd for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.52. Found: C, 55.31; H, 10.27; N, 21.62.

C. With Cinnamaldehyde.—An ether–diazomethane solution, prepared as described before, was distilled into a solution of cinnamaldehyde in ether. The product solution was sealed in a precooled pressure bottle and let stand for 2 days. Removal of the ether gave a high yield of crude product, but an attempt to distil this material resulted in decomposition of a considerable amount of the desired product. The distillate crystallized to light yellow crystals. Three recrystallizations from ether–petroleum ether gave colorless crystals, mp 100–101° [lit.[9] light yellow crystals, mp 101° (with some indication of lower melting Δ^1 isomer), prepared from benzalacetone and diazomethane]. The infrared spectrum in CCl_4 showed bands at 3400 (NH), 1720 (C=O), 1670 (conjugated C=O), 1545 (N=N), and 1410 cm^{-1}, indicating a mixture of the 1-pyrazoline and 2-pyrazoline isomers.

Registry No.—**1a**, 23936-71-2; **2a**, 23936-72-3; **2b**, 23936-73-4; **3a**, 23936-74-5; **3b**, 23936-75-6; **4a**, 23936-76-7; **4b**, 23936-77-8; 3-acetyl-3-methyl-1-pyrazoline, 1567-95-9; 3-acetyl-3-methyl-1-pyrazoline phenylhydrazone, 23936-79-0; diazomethane, 334-88-3; semicarbazone of 3-acetyl-3-methyl-1-pyrazoline, 23936-81-4; i, 23936-80-3.

Acknowledgment.—This research was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is made to the donors of this fund.

(9) L. I. Smith and K. L. Howard, *J. Amer. Chem. Soc.*, **65**, 165 (1943).

N Acylation of D-Glucosamine by a New Method

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N-Acyl derivatives of D-glucosamine are of great interest in biochemical studies. Several methods for the preparation of N-acyl derivatives of D-glucosamine have been reported in the literature.[2-7] The latest method reported by Inouye, *et al.*,[8] for preparing N-acyl derivatives of D-glucosamine required the treatment of a supersaturated solution of D-glucosamine hydrochloride in methanol with sodium methoxide solution followed by removal of precipitated sodium chloride before any acid chloride or anhydride was added for the reaction.

We wish to report here a new method for N acylation of D-glucosamine, in which *p*-nitrophenyl esters were used as acylating agents.

Bodanszky[9] first reported that amino groups of tyrosine and serine with unprotected hydroxyl groups could be selectively acylated by *p*-nitrophenyl esters. We found this reagent to be very effective for the N acylation of amino sugars. This method was found to be simple, direct, and more convenient than all previously reported methods.

Three typical N-acyl derivatives of D-glucosamine were prepared by using *p*-nitrophenyl esters of acetic, benzoic, and stearic acids.

Analytical data and physical constants for the three N-acyl-D-glucosamines prepared are given in Table I. All the three compounds show absorption maxima at 510, 545, and 585 nm when submitted to the Morgan Elson color reaction as reported previously.[10]

Experimental Section

Melting points were taken in open capillaries and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 521 infrared spectrophotometer, and absorption spectra in the visible range were obtained in Hilger Uvispeck spectrophotometer, Model H700. Optical rotations were measured with Hilger-Watts Model M-511 microptic photoelectric polarimeter.

Preparation of N-Acyl Derivatives of D-Glucosamine.—A representative experimental procedure is as follows. To a solution of *p*-nitrophenyl acetate (181 mg, 1 mmol) in 1.4 ml of freshly distilled dimethyl sulfoxide (DMSO) were added D-glucosamine hydrochloride (107 mg, 0.5 mmol) and triethylamine (0.07 ml, approx 0.5 mmol). Higher proportions of DMSO were required to dissolve *p*-nitrophenyl benzoate and *p*-nitrophenyl stearate. The mixture was stirred for 1 hr at room temperature, and, after standing for 4 days at 20°, the yellow mixture was diluted with 15 vol of dry methylene chloride (*ca.* ten times the volume of DMSO used). Excess of *p*-nitrophenyl acetate and triethylamine hydrochloride remained in solution and N-acetyl-D-glucosamine gradually separated out. The mixture was centrifuged after being allowed to stand for 2 hr, and the residue was washed twice with methylene chloride and three times with dry ether and finally dried over concentrated sulfuric acid. The yield was almsost quantitative. The crude material was crystallized from methanol by addition of ether to incipient turbidity.

Preparation of *p*-Nitrophenyl Stearate.—Stearic acid (2.3 g, 0.008 mol) was refluxed with thionyl chloride (3 ml, 0.04 mol) on water bath for 4 hr and kept overnight at 20°. Excess thionyl chloride was removed *in vacuo* at 100°. To the reaction product in the flask, dry pyridine (5 ml) was added while the flask was cooled in ice, and then, to this mixture, *p*-nitrophenol (2 g, 0.015 mol) in dry pyridine (10 ml) was added. Some solid appeared in the flask which was dissolved by heating to 50°. The reaction mixture was kept at 20° for 40 hr and then poured in crushed ice. The mixture was acidified to congo red with H_2SO_4, cooled in ice

(1) To whom correspondence should be addressed.

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(3) A. Neuberger and R. V. Pitt Rivers, *Biochem. J.*, **33**, 1580 (1939).
(4) T. White, *J. Chem. Soc.*, 428 (1940).
(5) A. S. Jones, M. A. G. Kaye, and M. Stacey, *ibid.*, 5016 (1952).
(6) W. R. Smithes, *Biochem. J.*, **53**, xxix (1953).
(7) S. Roseman and J. Ludowieg, *J. Amer. Chem. Soc.*, **76**, 301 (1954).
(8) Y. Inouye, K. Onodera, S. Kitaoka, and S. Hirano, *ibid.*, **78**, 4722 (1955).
(9) M. Bodanszky, *Nature*, **175**, 685 (1955).
(10) Y. Inouye, K. Onodera, and S. Kitaoka, *J. Agr. Chem. Soc. Jap.*, **29**, 139 (1955).

TABLE I
N-ACYL DERIVATIVES OF D-GLUCOSAMINE

Derivative	Mp, °C	[α]D	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ir (secondary amide), cm⁻¹ >C=O	Ir (secondary amide), cm⁻¹ >NH
N-Acetyl	206	+39.5[a]	q	$C_8H_{15}O_6N$	43.43	6.84	6.33	43.20	6.80	6.27	1625	3320
N-Benzoyl	198–200	+35.0[a]	q	$C_{13}H_{17}O_6N$	55.12	6.05	4.95	54.90	5.95	4.84	1630	3295
N-Stearoyl[b]	208	+24.3[c]	80	$C_{24}H_{47}O_6N$	64.68	10.63	3.14	64.53	10.50	2.95	1640	3300

[a] After 24 hr (c 2, water). [b] Inouye, *et al.*,[8] reported [α]D +78°. [c] After 24 hr (c 1, pyridine) (q stands for almost quantitative).

for 1 hr, and filtered. The product was washed with water and dried, yield 2.4 g. The crude product was dissolved in ethanol (100 ml) by boiling, decolorized with charcoal, and filtered hot. On cooling *p*-nitrophenylstearate crystallized in needles, mp 68.8°. *Anal.* Calcd for $C_{24}H_{39}O_4N$: C, 71.0; H, 9.69; N, 3.40. Found: C, 71.07; H, 9.69; N, 3.45.

p-Nitrophenyl acetate and *p*-nitrophenyl benzoate were prepared as reported previously.[11,12]

Registry No.—D-Glucosamine, 3416-24-8; *p*-nitrophenyl stearate, 14617-86-8; Table I (derivatives)—N-acetyl, 7512-17-6; N-benzoyl, 655-42-5; N-stearoyl, 24299-14-7.

Acknowledgments.—Our thanks are due to Mrs. C. Dutt of Indian Association for the Cultivation of Science, Calcutta, for the microanalysis and to Mr. S. Bhattacharya of Indian Statistical Institute, Calcutta, for technical assistance.

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Reduction of N-Chlorosulfonyl β-Lactams to β-Lactams with Sodium Sulfite

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Chlorosulfonyl isocyanate (CSI) has been shown to react with a variety of olefinic substances to give N-chlorosulfonyl β-lactams.[1-4] These compounds have been reduced by a variety of methods to β-lactams, the overall reaction serving as an important route to such compounds.

In general, the published procedures for the reduction step, (a) benzenethiol–pyridine in acetone at −30°,[5,6] (b) potassium iodide in aqueous sodium hydroxide,[1,5,6] (c) Raney nickel in ethanol,[5,6] aqueous hydrolysis,[5] and (d) 4 *N* KOH in acetone[7] or saturated methanolic KOH,[4] have suffered from variable yields because of reaction conditions under which some N-chlorosulfonyl β-lactams are not stable (methods b to d) and difficulties in separation of the desired lactams from biproducts (method a).[6]

In connection with a problem in which we required large quantities of seveal β-lactams, we decided to investigate the reduction of N-chlorosulfonyl β-lactams with an inorganic reducing agent such as sodium sulfite. This compound was an obvious choice since it has been known for some time that sodium sulfite is capable of reducing aliphatic and aromatic sulfonyl chlorides to the corresponding sulfinic acids.[8] In the case of N-chlorosulfonyl β-lactams such a reduction would give the N-sulfinic acid which could readily lose sulfur dioxide to afford the β-lactam.

Experimentally it was found that such reductions occurred within a few minutes and in high yield when a solution of the N-chlorosulfonyl β-lactam in ether or other suitable organic solvent was stirred with a 25% aqueous sodium sulfite solution at room temperature. The pH of the aqueous phase was kept slightly basic by addition of 10% KOH solution as the reduction proceeded. The advantages of the method are simplicity of the reaction and isolation procedures, easy adaptation to large-scale reactions, mild reaction conditions, and high yield of pure product. The reduction can be run at 0°, thereby allowing reduction of heat sensitive N-chlorosulfonyl lactams.

When pure N-chlorosulfonyl β-lactams were employed, near-quantitative yields of β-lactams could be isolated. In cases in which the N-chlorosulfonyl β-lactams were thermally unstable and difficult to isolate, *e.g.*, those derived from isoprene or butadiene,[2] the reduction was carried out at 0° on the crude CSI–olefin reaction product. The yields of β-lactam based on CSI were of the order of 70% (see Table I).

The structures assigned to the new lactams (from methylene cyclohexane and 1,3-cyclooctadiene) were those expected on the basis of a two-step reaction mechanism for the cycloaddition reaction;[1] they are, in addition, supported by spectroscopic and analytical data (see Experimental Section).

Experimental Section

Reactions of CSI with Olefins.—Known N-chlorosulfonyl β-lactams were prepared according to published procedures (see Table I).

CSI and 1,3-Cyclooctadiene.—Equimolar amounts of CSI and diene were heated overnight in benzene at 50°. The crude product obtained after washing the reaction mixture with water and evaporating the benzene layer was extracted twice with pentane to remove unreacted diene. The oily material so obtained (80%) was pure by thin layer chromatography (tlc). The infrared spectrum ($CHCl_3$) showed a strong band at 5.52 μ. Nmr peaks were at δ 1.2–2.5 (8 H), 3.4–4.0 (1 H), 5.1–5.5 (1 H), and 5.6–6.2 (2 H).

CSI and Methylenecyclohexane.—CSI (3.5 g) was added dropwise to 2.4 g of methylenecyclohexane in 10 ml of ether at 10°. The reaction mixture became semisolid with fine needles. The product was filtered and recrystallized from ether, yield 5.1 g (96%), mp 88–90°. The infrared spectrum showed the

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(2) E. J. Moriconi and W. C. Meyer, *Tetrahedron Lett.*, 3823 (1968).
(3) E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968); *J. Amer. Chem. Soc.*, **88**, 3657 (1966).
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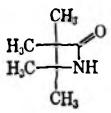
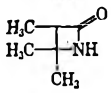
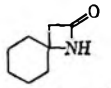
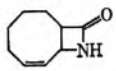
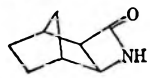
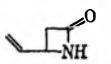
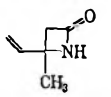
(5) R. Graf, *Ann.*, **661**, 111 (1963); *Org. Syn.*, **46**, 51 (1966).
(6) E. J. Moriconi and W. C. Crawford, *J. Org. Chem.*, **33**, 370 (1968).
(7) L. A. Paquette and T. Kakihana, *J. Amer. Chem. Soc.*, **90**, 3897 (1968).
(8) F. Muth in "Houben Weyl, Methoden der Organischen Chemie," Vol. 9, 4th ed, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1955, p 306.

TABLE I

REDUCTION OF N-CHLOROSULFONYL β-LACTAMS WITH Na_2SO_3

N-Chlorosulfonyl β-lactam prepared from	β-Lactam	Yield, %	Ref
2,3-Dimethyl-2-butene (a)		92	5
2-Methyl-2-butene (b)		98	5
Methylenecyclohexane (c)		98	
1,3-Cyclooctadiene (d)		97	
Norbornene (e)		77	3
1,3-Butadiene[a] (f)		72	2
Isoprene[a] (g)		68	2

[a] N-Chlorosulfonyl lactam was not isolated.

lactam band at 5.53 μ. Nmr absorption was at δ 1.0–2.8 (10 H) and 3.05 (s, 2 H).

Anal. Calcd for $C_8H_{12}ClNO_3S$: C, 40.4; H, 5.05; N, 5.90. Found: C, 40.17; H, 5.05; N, 5.82.

Reaction of N-Chlorosulfonyl β-Lactams with Na_2SO_3. General Procedure.—A solution of N-chlorosulfonyl β-lactam dissolved in ether was added slowly to a stirred mixture of about two parts 25% aqueous sodium sulfite and one part ether. The aqueous phase was kept slightly basic by addition of 10% KOH solution as the reduction proceeded. The reaction course could easily be followed by thin layer chromatography in which the product had a considerably smaller R_f value than the starting material. At the end of the reaction (usually less than 15 min) the ether layer was separated and dried and the solvent evaporated. The products were of greater than 95% purity as determined by nmr. The reduction could be carried out either at 25 or 0°.

1-Aza-2-keto[6.2.0]bicyclodec-8-ene.—N-Chlorosulfonyl β-lactam (2.25 g) was dissolved in 15 ml of ether and added to a mixture of 5 ml of ether and 10 ml of 25% aqueous sodium sulfite. The aqueous phase was kept between pH 7 and 8 by addition of 10% KOH solution. After 15 min tlc showed the absence of starting material and the formation of only one ether soluble product. The ether layer was separated and dried and the solvent was evaporated to yield 1.32 g (97%) of solid. Recrystallization from ethanol gave colorless granules: mp 100–101°; ir ($CHCl_3$) 5.71 μ; nmr ($CDCl_3$) δ 1.2–2.4 (8 H), 3.2–3.6 (1 H), 4.4–4.7 (1 H), 4.2–5.0 (2 H), and 6.8–7.2 (1 H).

Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.60; N, 9.26. Found: C, 71.12; H, 8.62; N, 9.10.

1-Azaspiro[3.5]nonan-2-one was prepared as above in 98% yield: colorless oil; bp 123° (4.2 mm); ir ($CHCl_3$) 5.72 μ; nmr ($CDCl_3$) δ 1.3–2.0 (10 H), 2.61 (d, J = 1.5 cps, 2 H, collapses to singlet on addition of D_2O), 7.3–8.0 (broad singlet 1 H).

Anal. Calcd for $C_8H_{13}NO$: C, 69.00; H, 9.34; N, 10.07. Found: C, 69.33; H, 9.39; N, 10.00.

Registry No.—Table I—lactam a, 17060-95-6; b, 24571-92-4; c, 24571-93-5; d, 24571-94-6; e, 24571-95-7; f, 22937-11-7; g, 20012-93-5; sodium sulfite, 7757-83-7; 1-azaspiro[3.5]nonan-2-one, 24571-98-0; 1-aza-2-keto[6.2.0]bicyclodec-8-ene, 24571-99-1.

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Evaluation of the σ* Parameter for Halodinitromethyl Groups

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Hine and Bailey[1] have determined the Taft σ* parameter for a number of polynitroalkyl groups and noted that the value of σ* for the trinitromethyl group, 4.54, is the largest recorded for an electrically neutral substituent. In connection with other studies, we required the σ* values for fluoro-, chloro-, and bromodinitromethyl substituents. We have evaluated the σ* parameter for these substituents by measuring the rates of reaction of the corresponding 4-halo-4,4-dinitrobutyric acids with diphenyldiazomethane in ethanol at 30°. These data are summarized in Table I.

TABLE I

RATE OF REACTION OF 4-Z-4,4-DINITROBUTYRIC ACID WITH DIPHENYLDIAZOMETHANE IN ETHANOL AT 30°

Z	k, M^{-1} min^{-1}
F	3.56 ± 0.04
Cl	3.36 ± 0.16[a]
Br	3.18 ± 0.03

[a] 2.97 ± 0.03 at 25°.

From these specific rate constants and the equation[1]

$$\log k = -0.105 + 1.174\,\sigma^*$$

we obtained σ* values for the 3-halo-3,3-dinitropropyl functions (Table II). Though the error in the value of k at 30° for 4-chloro-4,4-dinitrobutyric acid is unexplainedly about four times larger than that for the fluoro and bromo acids, measurements of the specific rate at 25° afforded a much more precise value of the rate constant for the chloro acid (Table I). Calculating σ* for the 3-chloro-3,3-dinitropropyl function from the 25° data gives a value which is essentially identical with the one obtained from the 30° rate data.

TABLE II

TAFT σ* PARAMETERS

R	σ*
$FC(NO_2)_2CH_2CH_2$	0.559 ± 0.005
$ClC(NO_2)_2CH_2CH_2$[a]	0.537 ± 0.017
$BrC(NO_2)_2CH_2CH_2$	0.517 ± 0.004
$FC(NO_2)_2$[b]	4.4
$ClC(NO_2)_2$[b]	4.2
$BrC(NO_2)_2$[b]	4.1

[a] σ* = 0.538 ± 0.005 from 25° data. [b] By multiplying σ* for $ZC(NO_2)_2CH_2CH_2$ by (2.8)[2].

Experimental Section

Preparation of 4-Halo-4,4-dinitrobutyric Acids.—The fluoro acid, prepared by hydrolyzing the corresponding methyl ester,[2] was obtained as colorless needles, mp 37–38°.

Chlorination and bromination of potassium methyl 4,4-dinitroburyrate in pentane afforded methyl 4-chloro- and methyl 4-

(1) J. Hine and W. C. Bailey, *J. Org. Chem.*, **26**, 2098 (1961).
(2) M. J. Kamlet and H. G. Adolph, *ibid.*, **33**, 3073 (1968).

bromo-4,4-dinitrobutyrate, respectively. The crude esters were hydrolyzed to the corresponding acids by refluxing with constant-boiling hydrochloric acid for 8 hr. Recrystallization of the crude acids from water gave 4-chloro-4,4-dinitrobutyric acid as a granular, white solid, mp 95.4–96.2°.

Anal. Calcd for $C_4H_5ClN_2O_6$: C, 22.6; H, 2.4; N, 13.2; Cl, 16.7. Found: C, 22.8, 22.9; H, 2.5, 2.4; N, 12.6, 12.5; Cl, 17.1, 16.8.

The 4-bromo acid, mp 90–91° (lit.[3] mp 88–89°), was obtained as glistening white plates.

Kinetic Procedure.—Measurements of the rates of reaction of these acids with diphenyldiazomethane were carried out as described previously.[4] The data summary in Table I results from at least five kinetic runs for each substrate.

Registry No.—4-Chloro-4,4-dinitrobutyric acid, 24057-18-9; 4-fluoro-4,4-dinitrobutyric acid, 15895-15-5; 4-bromo-4,4-dinitrobutyric acid, 5029-14-1; diphenyldiazomethane, 883-40-9.

Acknowledgment.—This work was supported by the Independent Research Fund of the U. S. Naval Ordnance Laboratory, Task IR-44.

(3) K. Klager, *J. Org. Chem.*, **16**, 161 (1951).
(4) H. E. Ruskie and L. A. Kaplan, *ibid.*, **30**, 319 (1965).

An Unusual Aspect of the Dimerization of N-Vinylcarbazole by Redox Reactions. The Participation of Molecular Oxygen

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The remarkable atypical features of polymerization on N-vinylcarbazole by either an ionic or a free-radical process have been recorded in a number of recent investigations. For example, it is difficult to present an adequate mechanism for the commercial preparation of poly-N-vinylcarbazole employing sodium chromate in hot aqueous dispersion or to account for the following observations when π-complex electron acceptors such as *p*-chloranil, tetracyanoethylene, and trinitrobenzene were used as initiators:[2,3] water (which normally inhibits ionic polymerization), thiophene (a potent retarder of conventional cationic propagation), and acrylonitrile (a material readily polymerized by radical or anionic species) each have qualitatively no effect on the polymerization of N-vinylcarbazole.

Also, it has been noted that conventional free-radical polymerization of this monomer initiated by azobisisobutyronitrile is sensitive to oxygen but unaffected by the presence of oxygen when π-complex electron acceptors are used as initiators.[4] Further, highly hindered phenols such as 2,6-di-*t*-butylphenol and 2,4-di-*t*-butylphenol, powerful inhibitors of free-radical chain reactions, do not retard but rather accelerate the azobisisobutyronitrile-initiated polymerization of N-vinylcarbazole in methanol.[5]

In an earlier study we have reported that ferric nitrate initiated polymerization of N-vinylcarbazole and 4-vinylpyridine proceeding by a one-electron transfer process[6] and that a dimer of N-vinylcarbazole, *trans*-1,2-dicarbazylcyclobutane, was among the products.[7] In extension of this study we have examined the reaction between N-vinylcarbazole and hydrogen peroxide, a redox couple analogous to the interaction between dimethylaniline and benzoyl peroxide,[8] which also afforded the dimeric product, *trans*-1,2-dicarbazylcyclobutane.

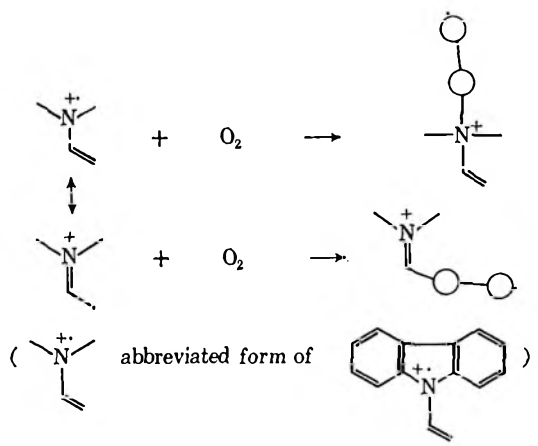
During the course of this investigation, we have found evidence of molecular oxygen participation in the formation of this dimer when either ferric nitrate or hydrogen peroxide is employed as an oxidant. In this note we wish to report our recent findings and suggest a role for molecular oxygen in the reaction sequence.

When reaction mixtures containing 5.0 mmol of N-vinylcarbazole and 0.05–0.5 mmol of ferric nitrate (hydrate) in methanol–water medium (9:1 v/v) were stirred at room temperature under nitrogen atmosphere over a period of 4 hr, they furnished some poly-N-vinylcarbazole of rather low molecular weight and a trace amount of dimer. The hydrolysis products of the monomer, carbazole, and acetaldehyde isolated as its 2,4-dinitrophenylhydrazone derivative were found to be the major products. In open air, for the same period of time, it afforded the same dimer in 15–20% of the theoretical yield in addition to the hydrolysis products. Under a stream of oxygen with 0.05–0.5 mmol of ferric nitrate the yield of the dimer was raised to 37–40%. Parallel observations were obtained when hydrogen peroxide was used as oxidant under comparable conditions. Under a nitrogen atmosphere, the yield of the dimer was practically nil with concentrations of hydrogen peroxide varying from 0.057 to 0.57 mmol. The bulk of the yield was found to be the hydrolysis products. In the presence of oxygen the dimer was obtained in 15–17% yield. The concentration of hydrogen peroxide in these reactions has no effect on the yield of the dimer. It is apparent that oxygen is not used in the regeneration of the oxidants but nevertheless essential in the formation of the dimer. It seems necessary for us to reexamine the mechanism of the dimer formation which we proposed in one of our earlier reports.

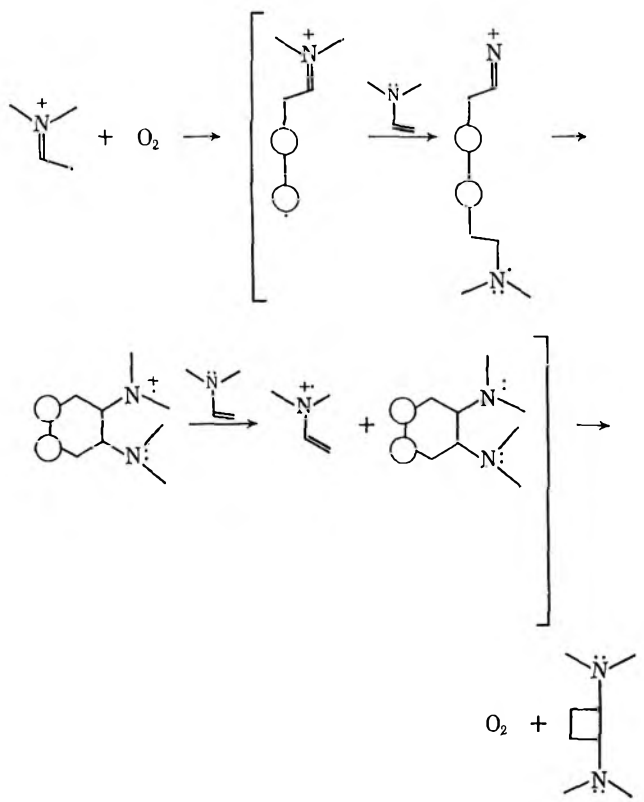
The interaction of molecular oxygen with free radicals is well known. The formation of the peroxy radical by oxygen with the intermediary radicals in this sequence of transformations should result in the forma-

(1) (a) To whom correspondence should be addressed; (b) Senior Honors Thesis, Wellesley College, 1968.
(2) L. P. Ellinger, *Chem. Ind.* (London), 1982 (1963).
(3) H. Scott, G. A. Miller, and M. M. Labes, *Tetrahedron Lett.*, No. 17, 1073 (1963).
(4) H. Scott, T. P. Konen, and M. M. Labes, *Polym. Lett.*, **2**, 689 (1964).
(5) C. H. Wang, unpublished results.
(6) C. H. Wang, *Chem. Ind.* (London), 751 (1964).
(7) S. McKinley, J. V. Crawford, and C. H. Wang, *J. Org. Chem.*, **31**, 1963 (1966).
(8) L. Horner and W. Kirmse, *Justus Liebigs Ann. Chem.*, **567**, 48 (1955).

tion of either a nitrogen peroxy radical, which is practically unknown, or the carbon peroxy radical.



The formation of carbon peroxy radical will eventually suppress the competitive reactions, namely, the hydrolysis of the N-vinyl group and the chain reaction of N-vinylcarbazole polymerization. It is also plausible that the carbon peroxy radical will add to the carbon–carbon unsaturation, which will lead to the formation of the six-membered ring peroxide intermediate and eventually to the final product.



The mechanism proposed is purely conjectural, since the isolation of the cylcic oxygen-containing intermediate was not fruitful and the detection of singlet oxygen was not carried out. However, the fact that no dimer formed when oxygen was excluded lends credence to the direct participation of molecular oxygen in the dimer formation.

Experimental Section[9]

Formation and Identification of the Dimer.—To a solution of 1 g (5.0×10^{-3} mol) of N-vinylcarbazole (Matheson Coleman and Bell), mp 67°, in 100 ml of 9:1 methanol–water, 0.02 g (5×10^{-5} mol) of ferric nitrate (Mallinckrodt), $Fe(NO_3)_3 \cdot 9H_2O$, was added. The mixture was stirred at room temperature in open air and a white precipitate gradually appeared. At the end of 4 hr the solid was collected. The yield was 0.25 g (*ca.* 25%): mp 189–192° (recrystallization from 1:1 ethanol–acetone raised the melting point to 191–193°); nmr δ_{TMS} 7–8.2 (16 H, aromatic), 6.26 (2 H, NCH), and 2.4–3.2 (4 H, methylene).

Anal. Calcd for $C_{28}H_{22}N_2$: C, 87.01; H, 5.74; N, 7.25; mol wt, 386.5. Found: C, 86.74; H, 5.80; N, 7.31; mol wt, 373 (Rast method, Nagy), 386 (mass spectrum).

All data correspond to the reported dimer, *trans*-1,2-dicarbazylcyclobutane.[10] Concentration of the filtrate by evaporation afforded 0.2 g of another white solid, which was identified as carbazole by melting point and by comparison of their infrared spectra. The mother liquid furnished acetaldehyde in *ca.* 20% yield based on the isolation of acetaldehyde 2,4-dinitrophenylhydrazone, mp 146–147° (lit.[11] mp 148°).

In other runs under identical conditions except with a gentle stream of oxygen, the yield of the dimer was 37–40% of the theoretical; the yield was not altered when the reaction was carried out at −10° instead of at room temperature. Efforts to detect the presence of peroxide intermediate in both cases failed. Under a stream of nitrogen only a trace amount of the dimer was obtained. The rest of the products were qualitatively identified as carbazole, acetaldehyde, and perhaps some low molecular weight poly-N-vinylcarbazole.

Increasing the amount of ferric nitrate up to tenfold in other runs did not substantially affect the corresponding yield of the dimer in the presence of either an oxygen or a nitrogen atmosphere.

Parallel experiments were carried out between N-vinylcarbazole and hydrogen peroxide. In a typical run, 2.25 ml (5.7×10^{-5} mol) of 0.06% hydrogen peroxide (Baker Analyzed reagent, 3% diluted to 0.06% with water) was added to a solution of 1 g (5.0×10^{-3} mol) of N-vinylcarbazole in 100 ml of 9:1 methanol–water solution. The solution was stirred at room temperature for 4 hr under a stream of (a) oxygen and (b) nitrogen and (c) in open air.

The experiments were worked up essentially in the same manner as in the previous ones. The yield of the dimer was *ca.* 10% in a, 0% in b, and *ca.* 3% in c. Change of the amount of hydrogen peroxide in each case did not alter the yield of the dimer to an appreciable degree.

Registry No.—*trans*-1,2-Dicarbazylcyclobutane, 1484-96-4.

(9) Elementary analysis was performed by M. S. Nagy, Massachusetts Institute of Technology. Melting points are not corrected. The nmr spectrum was recorded by using a Varian A-60 spectrometer from A. D. Little Analytical Laboratories. The mass spectrum was done by using a A.E.I. MS9 mass spectrometer with the generous help from Dr. G. Dudek, Harvard University.

(10) L. P. Ellinger, J. Fenney, and A. Ledwith, *Monatsh. Chem.*, **96**, 131 (1965).

(11) G. R. Clemo and W. H. Perkin, Jr., *J. Chem. Soc.*, **125**, 1804 (1924).

Sodium Arylsulfonates from Phenols

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Direct sulfonation of aromatic compounds often yields mixtures of isomeric sulfonic acids which are difficult to separate; however, sulfur-containing compounds of other types can be prepared free of isomers. Many can be oxidized to sulfonic acids.[1] The recently

(1) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience Publishers, New York, N. Y., 1965, p 201.

TABLE I
O-ARYL AND S-ARYL DIMETHYLTHIOCARBAMATES

Dimethylthiocarbamate	Mp, °C	Formula	Registry No.	Calcd, % N	Calcd, % S	Found, % N	Found, % S
O-Phenyl	Liquid	$C_9H_{11}NOS$	16241-04-6	7.73	17.69		
S-Phenyl	47–48	Same	7304-68-9			7.81	17.72
O-2,6-Dimethylphenyl	84–85	$C_{11}H_{15}NOS$	16241-12-6	6.69	15.32	6.68	15.24
S-2,6-Dimethylphenyl	42.5–43.5	Same	16241-13-7			6.71	15.19
O-2,6-Diisopropylphenyl	152.5–154	$C_{15}H_{23}NOS$	24010-73-9	5.28	12.08	5.34	12.02
S-2,6-Diisopropylphenyl	106.5–109	Same	24010-52-4			5.43	12.18

TABLE II
SODIUM ARYLSULFONATES

Aryl group	Yield, %	Formula	Registry No.	Calcd, % S	Calcd, % Na	Found, % S	Found, % Na
Benzene	63.5	$C_6H_5SO_3Na$	515-42-4	17.80	12.76	17.74	12.67
2,6-Dimethylbenzene	55.3	$C_8H_9SO_3Na$	24010-54-6	15.39	11.04	15.21	11.04
2,6-Diisopropylbenzene	57.7	$C_{12}H_{17}SO_3Na$	24010-55-7	12.13	8.70	12.24	8.80

TABLE III
DERIVATIVES OF ARYLSULFONIC ACIDS

	Sulfonamide					S-Benzylthiuronium salt				
		Calcd, %		Found, %			Calcd, %		Found, %	
Aryl group	Mp, °C	N	S	N	S	Mp, °C	N	S	N	S
Benzene	151–152[a]	8.91	20.40	8.63	20.44	147–148[b]	8.63	19.77	8.74	19.97
2,6-Dimethylbenzene[c]	114–115	7.56	17.31	7.65	17.09	160–161	7.95	18.19	7.86	17.96
2,6-Diisopropylbenzene[d]	125–126	5.80	13.28	5.58	13.10	200–201	6.85	15.69	6.88	15.84

[a] Lit. value, 150–150.5°: E. H. Huntress and J. S. Autenrieth, *J. Amer. Chem. Soc.*, **63**, 3446 (1941). [b] Lit. value, 147.5–148.5°: E. Chambers and G. W. Watt, *J. Org. Chem.*, **6**, 376 (1941). [c] Registry no.: for sulfonamide, 24010-56-8; for S-benzylthiuronium salt, 24010-58-0. [d] Registry no: for sulfonamide, 24010-57-9; for S-benzylthiuronium salt, 24010-59-1.

described Newman–Kwart rearrangement of O-aryl dimethylthiocarbamates to S-aryl dimethylthiocarbamates makes possible conversion of phenols into organic sulfur compounds with sulfur attached to the aromatic ring.[2] We now show these compounds capable of being oxidized to arylsulfonic acids. The overall scheme is illustrated below.

$$ArOH \longrightarrow ArOCSN(CH_3)_2 \xrightarrow{\Delta} ArSCON(CH_3)_2 \xrightarrow{[O]} ArSO_3H$$

Sodium benzenesulfonate, sodium 2,6-dimethylbenzenesulfonate, and sodium 2,6-diisopropylbenzenesulfonate were prepared to illustrate the method. Correct melting points for benzenesulfonamide and S-benzylthiuronium benzenesulfonate confirm that benzenesulfonic acid is produced by oxidizing S-phenyl dimethylthiocarbamate. Preparing sodium 2,6-dimethylbenzenesulfonate and sodium 2,6-diisopropylbenzenesulfonate shows that compounds not readily available by other procedures can be synthesized easily. Preparation of the latter demonstrates that hindered sodium arylsulfonates can be made.

The O-aryl and the S-aryl dimethylthiocarbamates were prepared by the method described by Newman and Karnes.[2] Melting points and elemental analyses of these compounds are given in Table I. Since O-phenyl dimethylthiocarbamate is a liquid, purification by recrystallization is not possible, and, since it is thermally unstable, distilling would lead to rearrangement. Physical constants are, therefore, not available for the compound.

Oxidation of the S-aryl compounds to the arylsulfonic acids was accomplished using 30% hydrogen peroxide as the oxidizing agent and formic acid as the solvent. A similar procedure was used by Yoder for oxidizing isothiuronium derivatives of steroids.[3] After the oxidation reaction was complete, formic acid was removed. The arylsulfonic acid was taken up in water, and the pH was adjusted to 9 using 1 *N* sodium hydroxide solution. Water was removed by evaporating, and sodium arylsulfonate remained. Base must be added during evaporation of the water to ensure removal of dimethylamine resulting from incomplete oxidation. Products were purified by recrystallizing until further purification produced no change in infrared spectrum. Yields and results of elemental analyses are shown in Table II. In order to characterize the sodium arylsulfonates, S-benzylthiuronium derivatives and arylsulfonamides were prepared. Melting points of the derivatives of sodium benzenesulfonate agree with those reported in the literature. Elemental analyses of derivatives of the other sulfonates are satisfactory. These are given in Table III.

Work reported here demonstrates that hydroxyl groups of phenols can be replaced by sulfonate groups even in the case of phenols as hindered as 2,6-diisopropylphenol. Since many techniques are available for preparing variously substituted phenols, the procedure reported here makes possible the synthesis of a wide variety of sulfonic acids free of isomeric impurities.

Experimental Section

Melting points were taken using a capillary melting point apparatus and are corrected. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. Phenol was Baker Analyzed; 2,6-dimethylphenol and 2,6-diisopropylphenol were obtained from Aldrich Chemical Co.

Preparation of Sodium 2,6-Diisopropylbenzenesulfonate.—To a 2000-ml, round-bottom flask was added a solution of 63.2 g

(2) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).

(3) L. Yoder, *ibid.*, **20**, 1317 (1955).

(0.238 mol) of S-2,6-diisopropylphenyl dimethylthiocarbamate in 1000 ml of formic acid. The solution was stirred with a magnetic stirrer as 365 ml of 30% hydrogen peroxide was added dropwise. The mixture was stirred overnight. Formic acid was removed under vacuum using a rotary evaporator. The 2,6-diisopropylbenzenesulfonic acid was taken up in water, and the pH was adjusted to 9 using 1 *N* NaOH solution. The water was removed by evaporating on a steam bath. The pH was checked periodically during the evaporation and was maintained at 9 by adding 1 *N* NaOH solution. Sodium 2,6-diisopropylbenzenesulfonate was recrystallized several times by being dissolved in water and precipitated by saturating the solution with NaCl at the boiling point. The white crystalline product was dried in an 80° vacuum oven. A yield of 36.3 g (0.137 mol, 57.7%) of product was obtained.

The Acid-Catalyzed Nitramine Rearrangement. V. The Effect of Isotopic Replacement of Aromatic Ring Hydrogens[1-3]

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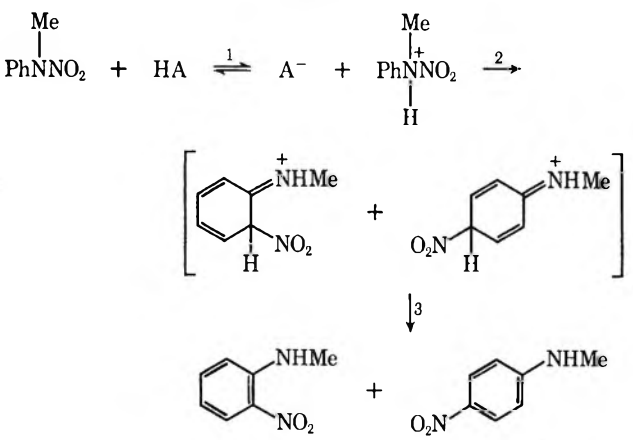
The detection of specific acid catalysis for the aromatic nitramine rearrangement[1b] showed that the rate-determining process in this reaction followed the protonation step. The observed substituent effects[1c] suggested that the breaking of the amine–nitro group bond (Chart I, step 2) was rate limiting. To substantiate this latter assignment, it was desirable to rule out proton loss (step 3) as being significant in rate or product determination. This was accomplished by examining the reactivity of nitramines in which the aromatic hydrogens were replaced by deuterium or tritium atoms.

CHART I



Rates and product distributions were determined for N-nitro-N-methylaniline and N-nitro-N-methylaniline-2,6-d_2 and for N-nitro-N-methyl-*p*-toluidine and N-nitro-N-methyl-*p*-toluidine-2-*t*. The results are listed in Table I. It is obvious that deuterium or tritium substitution at the migration terminus did not affect either the rate of rearrangement or the distribution of products.

TABLE I

EFFECT OF ISOTOPIC REPLACEMENT OF AROMATIC-RING HYDROGENS ON THE AROMATIC NITRAMINE REARRANGEMENT

Compd	10^3k, sec^{-1}	*ortho*,[c] %	*para*,[d] %
N-Nitro-N-methylaniline[a]	1.63 ± 0.04	47.9 ± 1.4	29.3 ± 0.1
N-Nitro-N-methylaniline-2,6-d_2[a]	1.66 ± 0.07	47.8 ± 1.0	29.9 ± 0.5
		% 2-H[e]	% 2-t[f]
N-Nitro-N-methyl-*p*-toluidine[b]	2.65 ± 0.03	100	...
N-Nitro-N-methyl-*p*-toluidine-2-*t*[b]	2.69 ± 0.03	48 ± 2	52 ± 2

[a] Rearrangement was carried out at 40.0° in 0.511 *M* aqueous $HClO_4$ containing 0.500 *M* $NaClO_4$. [b] Rearrangement was carried out at 20.0° in 0.204 *M* aqueous $HClO_4$ containing 0.807 *M* $NaClO_4$. [c] Per cent of 2-nitro-N-methylaniline in the product. [d] Per cent of 4-nitro-N-methylaniline in the product. [e] Per cent of 2-nitro-N-methyl-*p*-toluidine in the nitrated product. [f] Per cent of 2-nitro-N-methyl-*p*-toluidine-2-*t*-in the nitrated product.

These results demonstrate that proton loss (step 3) is not involved in determining the rate of the overall reaction and that, in fact, proton loss must be a relatively fast, facile, low activation energy step in comparison with other changes that occur in the forward progress of the reaction. The first of these points is proved by the finding that the rate of appearance of product was not at all affected by isotopic substitution. If the activation energy of step 3 was of significant magnitude, then the pentadienimine cation intermediate should accumulate and the rate of product formation should be determined by its decomposition. Since its breakdown depends on the scission of a carbon–hydrogen bond, the process should be slowed if a C–D bond replaces the original C–H bond, and the rate of production of nitroanilines from normal and deuterated nitramines should have been different. This result also supports the finding of specific acid catalysis in the nitramine rearrangement, since rate-limiting proton loss (step 3) would have led to general acid catalysis.

It has been suggested that an *ortho* pentadienimine cation intermediate intervenes between the protonated nitramine and the *para* pentadienimine cation[4,5] (Chart II). If the rearrangement follows such a pathway and step 2 is rate determining, then no rate effect of isotopic substitution would be observed. However, if step 4 was reversible or similar in rate to step 5, deuteration of the 2,6 positions of N-nitro-N-methylaniline should lead to a higher proportion of *p*-nitro-N-methylaniline in the product, since C–D bonds are hard to break and step 5 would be retarded. Alter-

(1) Previous papers in this series: (a) W. N. White, D. Lazdins, and H. S. White, *J. Amer. Chem. Soc.*, **86**, 1517 (1964); (b) W. N. White, C. Hathaway, and D. Huston, *J. Org. Chem.*, **35**, 737 (1970); (c) W. N. White and J. R. Klink, *J. Org. Chem.*, **35**, 965 (1970).

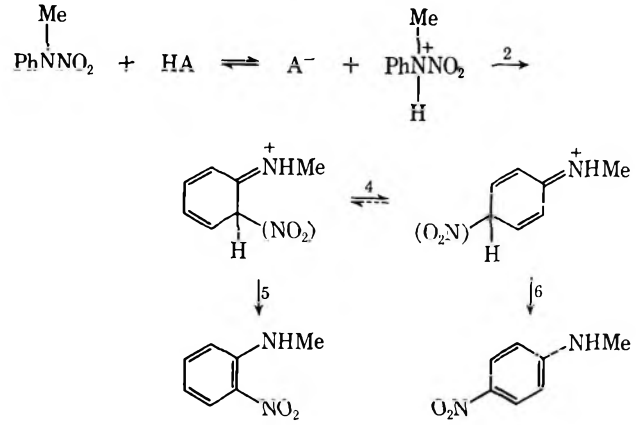
(2) Part of this work has been reported in preliminary form: W. N. White, J. R. Klink, D. Lazdins, C. Hathaway, J. T. Golden, and H. S. White, *J. Amer. Chem. Soc.*, **83**, 2024 (1961).

(3) This work was supported by Grants G-7345 and GP-1970 from the National Science Foundation.

(4) S. Brownstein, C. A. Bunton, and E. D. Hughes, *J. Chem. Soc.*, 4534 (1958).

(5) M. J. S. Dewar in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 306–313.

CHART II



natively, if step 4 was much faster than step 5, no *o*-nitro-N-methylaniline would be formed at all or, if step 5 was more rapid than step 4, no *p*-nitro-N-methylaniline would be produced. None of these possibilities is realized experimentally—N-nitro-N-methylaniline and its 2,6-dideuterio derivative rearrange at the same rate to give an identical product consisting of both *o*- and *p*-nitro-N-methylaniline. Thus the mechanism of Chart II is incorrect—both *o*- and *p*-nitro-N-methylaniline must be formed from an intermediate whose partition is not determined by the ease of hydrogen loss. The latter process must occur readily and have a low activation energy.

Negligible isotope effects are expected for reactions with very low activation energies in which the transition state resembles the initial state. Thus step 5 might not be subject to an isotope effect if its activation energy was sufficiently small. However, if significant amounts of *para* isomer are to be formed by the Chart II mechanism, then step 4 would have to have a rate and an activation energy similar to those of step 5. A very low activation energy for an isomerization such as step 4 is quite improbable. Thus the lack of an isotope effect must be attributed to the inadequacy of the mechanism of Chart II.

A similar conclusion can be derived from the behavior of N-nitro-N-methyl-*p*-toluidine and its 2-tritiated derivative. Hydrogen loss from the tritiated position would be slowed so that the nitro group migration to the 4 position would be relatively favored in the mechanism of Chart II. From that point the nitro group may move back unselectively to either of the *ortho* positions or be lost from the molecule. The results would be the same in either case—the N-methyl-2-nitro-4-toluidine formed would contain more tritium than anticipated for statistical replacement of the hydrogens in the *ortho* positions. Since the mechanism of Chart II leads to a conclusion contrary to the observed results, the mechanism must be in error.

These results show that aromatic ring proton loss in the acid-catalyzed nitramine rearrangement is a fast, low activation energy, kinetically insignificant process. This proves that any σ-bonded intermediates formed from the aromatic nitramine rapidly lose protons to reform the benzenoid system. Thus such intermediates cannot intervene as "stepping stones" to other intermediates of the same type, as has been proposed in several mechanisms for the aromatic nitramine rearrangement.[4,5]

Experimental Section

p-Iodoaniline-2,6-d_2.—A well-stirred mixture of 7.08 g of aniline-2,4,6-d_3,[6] 70 ml of water, and 9.64 g of sodium bicarbonate was treated with 16.38 g of iodine (in 1-g portions) over a period of 45 min. The temperature was kept at 10° during the addition. The mixture was then stirred at room temperature for 25 min. The aqueous layer was decanted off and the residue was washed several times with water by decantation. The remaining solid was extracted four times with 100-ml portions of boiling petroleum ether (bp 30–60°). Concentration of these extracts afforded 8.8 g (35%) of light tan crystals, mp 60.0–60.5° (lit.[7] mp 60°). A small sample for analysis was purified by sublimation and recrystallized from petroleum ether.

Aniline-2,6-d_2.—To a solution of 7.00 g of *p*-iodoaniline-2,6-d_2 in 10 ml of dry ether was added 175 ml of 0.50 *N* *n*-butyllithium in ether. After 5 min, the solution was cooled in an ice bath and a solution of 35 ml of concentrated hydrochloric acid in 35 ml of water was added as rapidly as possible. The resulting mixture was concentrated to 20 ml, made basic with 10% sodium hydroxide, and extracted with ether. The combined extracts were dried over potassium carbonate and the ether was distilled off through a helices-packed column using a water bath at 50–55°. The residual material was distilled to yield 1.48 g (21%) of aniline-2,6-d_2 as a clear, colorless liquid, bp 100° (25 mm) [lit.[8] bp 119.4° (100 mm)].

N-Nitro-N-methylaniline-2,6-d_2.—This compound was prepared by alkaline nitration[9] of aniline-2,6-d_2.

p-Toluidine-2-*t*.—A solution of 2.68 g of *p*-toluidine hydrochloride in 3 ml of tritiated water was heated at 85° for 24 hr. The water was then evaporated. The residual solid was dissolved in 5 ml of ordinary water and the resulting solution was freeze dried. This treatment with ordinary water was repeated four times. The free amine was precipitated from a filtered aqueous solution by addition of 5% sodium hydroxide solution. The solid was collected by filtration, washed with water, and dried. There was obtained 1.66 g (83%) of crude *p*-toluidine-2-*t*, mp 34–35° (lit.[10] mp 42.8°). This material was combined with 3.25 g of normal *p*-toluidine and the mixture was crystallized from petroleum ether to give 4.7 g of colorless plates, mp 42.5–43.5°.

The 2,6-dibromo derivative was prepared by bromination of the amine in acetic acid. It was crystallized from petroleum ether as white plates, mp 78–79° (lit.[11] mp 79°).

N-Nitro-N-methyl-*p*-toluidine-2-*t*.—This substance was obtained by alkaline nitration[9] of *p*-toluidine-2-*t*.

Rearrangement of N-Nitro-N-methyl-*p*-toluidine-2-*t*.—In a typical reaction, 100.0 ml of 1.022 *M* perchloric acid, 110.30 g (0.900 mol) of sodium perchlorate, and 5.0 g of sulfamic acid were placed in a 1-l. volumetric flask. Sufficient water was added to bring the volume to *ca.* 980 ml. The flask was then thermostatted for 45 min at 20° and a solution of 125.1 mg of N-nitro-N-methyl-*p*-toluidine-2-*t* in 10.0 ml of dioxane was added. The contents were mixed and the volume was brought to 1 l. by addition of water. The mixture was kept at 20° for 90 min.

After adjustment of the pH of the mixture to *ca.* 8.5 with sodium hydroxide, it was extracted four times with 100-ml portions of ether. The extracts were evaporated and the residue was dissolved in 3 ml of carbon tetrachloride and chromatographed on a 26 × 170 cm neutral alumina (activity grade II) column using 1:1 diethyl ether–petroleum ether as eluent. The product was eluted by *ca.* 200 ml of the developer. The solvent was evaporated and the residue was recrystallized twice from petroleum ether to yield 92 mg of red-orange N-methyl-2-nitro-4-toluidine-6-*t*, mp 82–83° (lit.[12] mp 84–85°).

The acetyl derivative of this amine was used in the radioactivity assays. It was prepared by warming the amine with acetic anhydride and a trace of sulfuric acid. The product, thrice recrystallized from petroleum ether, melted at 64.0–64.5° (lit.[13] mp 64°).

Deuterium Analysis.—*p*-Iodoaniline-2,6-d_2, aniline-2,6-d_2, and

(6) Prepared by the procedure described by A. Murray, III, and D. C. Williams, "Organic Synthesis with Isotopes," Interscience Publishers, New York, N. Y., 1958, p 1441.
(7) A. W. Hoffman, *Justus Liebigs Ann. Chem.*, **67**, 65 (1848).
(8) G. W. A. Kehlbaum, *Z. Phys. Chem.*, **26**, 601 (1898).
(9) W. N. White, E. F. Wolfarth, J. R. Klink, J. Kindig, C. Hathaway, and D. Lazdins, *J. Org. Chem.*, **26**, 4124 (1961).
(10) W. H. Perkin, *J. Chem. Soc.*, **69**, 1209 (1896).
(11) K. Fries, *Justus Liebigs Ann. Chem.*, **346**, 166 (1906).
(12) A. Gatterman, *Chem. Ber.*, **18**, 1482 (1885).
(13) S. Niementowski, *ibid.*, **20**, 1876 (1887).

N-nitro-N-methylaniline-2,6-d_2 were assayed for their deuterium content by the falling-drop method.[14] The sample was burned to water by vaporizing it into a stream of oxygen which carried the vapors first over the decomposition product of silver permanganate (at 550°) and then over the decomposition product of potassium permanganate. The condensed water was diluted quantitatively with ordinary water so that the final sample contained *ca.* 0.4 at. % deuterium. The drop time in isobutyl benzoate was measured and compared with the drop times for standard D_2O–H_2O mixtures to obtain the atom per cent deuterium in the sample. The standard deviation of the measurement was *ca.* ±0.8%. Three determinations were made on each sample.

The isotopic purity of the various samples follows: *p*-iodoaniline-2,6-d_2, 1.82 D atoms; aniline-2,6-d_2, 1.83 D atoms; and N-nitro-N-methylaniline-2,6-d_2, 1.80 D atoms. These results were verified through independent analyses by a commercial laboratory.[15]

Radioactivity Assays.—*p*-Toluidine-2-*t*, 2,6-dibromo-4-toluidine (prepared from the *p*-toluidine-2-*t*), N-nitro-N-methyl-*p*-toluidine-2-*t*, and the rearrangement product, N-methyl-2-nitro-4-toluidine-6-*t*, were assayed for tritium content by liquid scintillation counting. The scintillator solution contained PPO and POPOP dissolved in an ethanol (23%)–toluene (77%) mixture. Carefully weighed samples of the tritiated compounds were dissolved in aliquots of the scintillator solution and the resulting sample solutions were counted.

To correct for differential quenching effects of the various compounds assayed, 1 ml of a solution of ethanol-*t* in toluene was added to each sample after counting and also to a blank containing only scintillator solution. The samples were then recounted. By comparing the increases in activity of the samples to that of the blank, the extent of quenching could be estimated and the actual sample counts could be corrected for this phenomenon.

Relative activities were calculated from the counts per minute per millimole using the average activity of N-nitro-N-methyl-*p*-toluidine as a standard of comparison. The average relative activities follow: *p*-toluidine-2-*t*, 1.03 ± 0.03; 2,6-dibromo-4-toluidine, 0.00 ± 0.00; N-nitro-N-methyl-*p*-toluidine, 1.00 ± 0.02; and N-methyl-2-nitro-4-acetotoluide-6-*t*, 0.52 ± 0.02.

Rates of Rearrangement of Aromatic Nitramines.—The methods described in previous papers[1b,c] in this series were utilized to determine the kinetic constants for the acid-catalyzed rearrangements of N-nitro-N-methylaniline, N-nitro-N-methylaniline-2,6-d_2, N-nitro-N-methyl-*p*-toluidine, and N-nitro-N-methyl-*p*-toluidine-2-*t*.

Spectrophotometric Analysis of Rearrangement Products.—The percentages of *o*- and *p*-nitro-N-methylaniline obtained from N-nitro-N-methylaniline and from N-nitro-N-methylaniline-2,6-d_2 were determined as described previously.[1a] The quoted results (Table I) are the average of two determinations.

Registry No.—N-Nitro-N-methylaniline, 7119-93-9; N-nitro-N-methylaniline-2,6-d_2, 23998-84-7; N-nitro-N-methyl-*p*-toluidine, 23042-30-0; N-nitro-N-methyl-*p*-toluidine-2-*t*, 23998-86-9.

(14) H. C. Barbour and W. F. Hamilton, *J. Biol. Chem.*, **69**, 625 (1926); J. Horacek, *Collect. Czech. Chem. Commun.*, **26**, (3), 772 (1961).
(15) Josef Nemeth, Urbana, Ill.

Absolute Configuration of 1-Methylalkylamines

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During a study of structure–taste relationships of substituted isoasparagines,[1,2] we were surprised to observe a reversal of configurational requirements for sweetness. Thus, in compounds where R_1 was methyl or methoxycarbonyl and R_2 was cyclohexyl or an aromatic ring, only the LL isomer was sweet. However, in the case of R_1 = methyl and R_2 = *n*-butyl or isobutyl the sweet isomer was LD. It seemed highly unlikely that in a biochemical reaction involving complexing between an optically active substrate and an enzyme site conformational specificity could be reversed by a change from cyclohexyl to *n*-butyl when the structural alteration was insulated from the asymmetric carbon by a methylene group. We were led, therefore, to reexamine the absolute configurations previously assigned to 1-methylhexylamine and 1,4-dimethylpentylamine.[3]

$$H_2NCH(CH_2CO_2H)CONHCH(R_1)CH_2R_2$$

For the sake of consistency with the literature, the designations L and D will be retained. It must be understood that for 1-methylalkylamines the assumption is implicit that the methyl group represents the carboxyl group of the corresponding amino acid and the alkyl group represents the amino acid side chain. This is true whether or not the amino acid so described exists in nature or not. The Cahn–Ingold–Prelog[4] system involves a different assumption, namely, agreement on the sequence rules. For amino acids L = *S*, but for the derived 1-methylalkylamines L = *R* which might introduce an element of confusion. However, for some of the compounds to be described the Cahn–Ingold–Prelog designation allows the argument to be followed with greater facility. Both systems will therefore be used in the present work.

L-Leucine has been related to 1,3-dimethylbutylamine having a positive rotation in methanol.[5] This amine is the closest analog to higher 1-methylalkylamines that can be derived from a naturally occurring amino acid. Resolution of 1,3-dimethylbutylamine, 1-methylhexylamine, and 1,4-dimethylpentylamine was achieved by fractional crystallization of the L-(+)-tartrates.[6] The bases were regenerated and distilled and rotations measured both neat and in methanol. The neat rotations were all negative; 1,3-dimethylbutylamine had a positive rotation in methanol while 1-methylhexylamine and 1,4-dimethylpentylamine had negative rotations in methanol. Treatment of resolved 1,3-dimethylbutylamine with *p*-toluenesulfonyl chloride in pyridine gave an amide identical with that obtained from L-leucine.

As further evidence for absolute configuration of the seven-carbon amines, partial resolution[7,8] of 2-phenylbutyric acid was carried out. The absolute configuration of this acid is *S*-(+).[7] If an excess of an optically inactive acid is caused to react with an optically active amine and the transition state is similar to the final product, then the resulting mixture of diastereoisomeric amides will contain an excess of the amide representing the least hindered transition state. The product can be analyzed easily by isolating unreacted

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(2) R. H. Mazur, A. H. Goldkamp, P. A. James, and J. M. Schlatter, *J. Med. Chem.*, in press.
(3) B. Halpern, J. Ricks, and J. W. Westley, *Chem. Commun.*, 679 (1966).
(4) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Int. Ed. Engl.*, **5**, 385 (1966).
(5) P. Karrer and P. Dinkel, *Helv. Chim. Acta*, **36**, 122 (1953).
(6) F. G. Mann and J. W. G. Porter, *J. Chem. Soc.*, 456 (1944).
(7) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962).
(8) O. Cervinka, *Collect. Czech. Chem. Commun.*, **31**, 1371 (1966).

acid and finding its sign of rotation. This acid is the isomer giving the most hindered transition state and, if the absolute configuration of the acid is known, the absolute configuration of the amine can often be deduced.

Coupling of the three amines with an excess of 2-phenylbutyric acid gave, in each case, recovered acid with a positive neat rotation and positive rotation in methanol. Since the structural changes among the three amines are not likely to alter group interactions in the 2-phenylbutyramides, 1-methylhexylamine and 1,4-dimethylpentylamine have the same absolute configuration as 1,3-dimethylbutylamine, namely *R*-(−) referred to neat rotations. As was mentioned above, in this series of amines *R* = L and taste turned out to be a reliable guide to absolute configuration.

Experimental Section

Elemental analyses were done under the direction of E. Zielinski and rotations under the direction of A. J. Damascus. Melting points were determined in a stirred bath and are uncorrected.

Resolutions.—1,3-Dimethylbutylamine (101 g, 1.0 mol) and 150 g (1.0 mol) of L-(+)-tartaric acid were dissolved in 600 ml of methanol, and the solution allowed to stand overnight at room temperature. The product (98.2 g) was crystallized three times from 2.5 parts of methanol to yield 41.2 g of the tartrate salt, mp 128–131°, $[\alpha]^{28}D$ +21.0° (*c* 1, MeOH). *Anal.* Calcd for $C_{10}H_{21}NO_6 \cdot {}^1/_3H_2O$: C, 46.68; H, 8.49; N, 5.44. Found: C, 46.91; H, 8.50; N, 5.46.

The above tartrate (30.2 g, 0.12 mol) was suspended in 150 ml of ether plus 50 ml of water. Sodium hydroxide (50%, 20 ml, 0.36 mol) was added and the mixture shaken vigorously. The ether layer was washed with 25 ml of 5 *M* potassium carbonate, and dried over anhydrous potassium carbonate; the ether was distilled. The residue was fractionated to yield 9.96 g (82%) of 1,3-dimethylbutylamine: bp 106–107°; $[\alpha]^{25}D$ −11.2° (neat), +3.5° (*c* 1, MeOH) [lit.[9] −10.7° (neat)]. *Anal.* Calcd for $C_6H_{15}N$: N, 13.84. Found: N, 13.65.

1-Methylhexylamine tartrate had mp 109–110°; $[\alpha]^{26}D$ +19.0° (*c* 1, MeOH). *Anal.* Calcd for $C_{11}H_{23}NO_6$: C, 49.80; H, 8.74; N, 5.28. Found: C, 49.53; H, 8.90; N, 5.12.

The free base had bp 140°; $[\alpha]^{25}D$ −6.7° (neat), −0.8° (*c* 10, MeOH). *Anal.* Calcd for $C_7H_{17}N$: N, 12.16. Found: N, 12.21.

1,4-Dimethylpentylamine tartrate had mp 142–144°; $[\alpha]^{28}D$ +19.5° (*c* 1, MeOH). *Anal.* Calcd for $C_{11}H_{23}NO_6$: C, 49.80; H, 8.74; N, 5.28. Found: C, 49.79; H, 8.90; N, 5.12.

The free base had bp 133°; $[\alpha]^{25}D$ −7.2° (neat), −0.6° (*c* 10, MeOH). *Anal.* Calcd for $C_7H_{17}N$: N, 12.16. Found: N, 12.48.

N-*p*-Toluenesulfonyl-L-1,3-dimethylbutylamine.—L-Leucinol N-*p*-toluenesulfonamide O-*p*-toluenesulfonate[5] (8.50 g, 0.02 mol), mp 105–107°, $[\alpha]^{25}D$ −54.1° (*c* 1, MeOH), was reduced with $LiAlH_4$ in refluxing ether. Crystallization of the crude product from *n*-pentane gave the desired amide, 3.29 g (65%), mp 65–67°, $[\alpha]^{25}D$ +3.8° (*c* 1, MeOH); lit.[5] mp 62–63°, $[\alpha]^{18}D$ +1.4° (*c* 0.8, EtOH).

Resolved 1,3-dimethylbutylamine (1.0 g, 0.01 mol) was treated with *p*-toluenesulfonyl chloride in pyridine. Crystallization of the crude product from *n*-pentane yielded the toluenesulfonamide, 2.03 g (80%), mp 65–67°, $[\alpha]^{28}D$ +4.5° (*c* 1, MeOH).

Anal. Calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.29; N, 5.49; S, 12.56. Found: C, 61.45; H, 8.14; N, 5.78; S, 12.73.

Asymmetric Syntheses.—Racemic 2-phenylbutyric acid (9.84 g, 0.06 mol) was dissolved in 50 ml of methylene chloride, and 4.04 g (0.04 mol) of resolved 1,3-dimethylbutylamine was added. The mixture was stirred in an ice bath and 8.24 g (0.04 mol) of dicyclohexylcarbodiimide in 40 ml of methylene chloride was added. After stirring 0.5 hr at room temperature, the dicyclohexylurea was removed by filtration and the methylene chloride distilled. The residue was dissolved in ether and extracted with 50 ml of 1 *N* sodium hydroxide. The basic extract was acidified with hydrochloric acid and the unreacted 2-phenylbutyric acid taken up in ether; the ether extract was washed twice with water, dried over sodium sulfate, and distilled. The residue was dried overnight at room temperature under vacuum. Recovered 2-phenylbutyric acid (3.40 g, 0.0207 mol) had $[\alpha]^{27}D$ +7.4° (neat), +6.3° (*c* 10, MeOH).

When optically active 1-methylhexylamine was used, unreacted 2-phenylbutyric acid showed $[\alpha]^{26}D$ +7.3° (neat), +5.7° (*c* 10, MeOH).

When optically active 1,4-dimethylpentylamine was used, unreacted 2-phenylbutyric acid had $[\alpha]^{27}D$ +8.4° (neat), +6.5° (*c* 10, MeOH).

Registry No.—1-Methylhexylamine, 6240-90-0; 1-methylhexylamine tartrate, 24118-68-1; 1,4-dimethylpentylamine, 24110-97-2; 1,4-dimethylpentylamine tartrate, 24215-84-7; 1,3-dimethylbutylamine tartrate, 24118-69-2; 1,3-dimethylbutylamine toluene sulfonamide, 24118-70-5.

(9) R. H. Holm, A. Chakravorty, and G. O. Dudek, *J. Amer. Chem. Soc.*, **86**, 379 (1964).

Reaction of Perfluoro Olefins with Bromine Trifluoride in Bromine

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Bromine trifluoride has been used as a source of BrF in organic reactions; however, the references are few.[3,4] Chambers, *et al.*,[5] have reported the addition of BrF to hexafluoropropene to give the 2-bromo derivative. No information is available concerning such reactions with more complex perfluoro olefins. The present investigation concerns the reactions of bromine trifluoride in bromine with some perfluoroheptenes and hexenes. Davis and Larsen,[6] using BrF_3 in the presence of a large excess of Br_2, have replaced Br by F in bromofluoroethanes. In the present study no perfluoroalkanes were found. The major products of the reactive olefins are the perfluoroalkyl monobromides.

Perfluoroheptene-1 gave almost exclusively perfluoro-2-bromoheptane (87%). Other fractions isolated in small amounts were perfluoro-*trans*-2-bromoheptene-2 (4%) and perfluoro-*trans*-2-bromohexene-2 (9%). Perfluoroheptane and 1-bromoheptane were absent in the crude product as shown by vpc analysis. Perfluoroheptene-2,[7] synthesized by treating perfluoroheptene-1 with cesium fluoride,[8] gave a mixture of 50:50 perfluoro-2-bromo- and -3-bromoheptanes.

The reaction of BrF_3 in Br_2 with the three isomeric

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(3) W. K. R. Musgrave, *Advan. Fluorine Chem.*, **1**, 12 (1960).

(4) E. T. McBee, V. V. Lindgren, and W. B. Ligett, *Ind. Eng. Chem.*, **39**, 378 (1947).

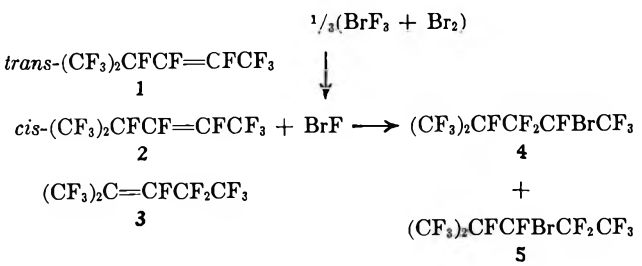
(5) R. D. Chambers, W. K. R. Musgrave, and J. Savory, *Proc. Chem. Soc. London*, 113 (1961).

(6) R. A. Davis and E. R. Larsen, *J. Org. Chem.*, **32**, 3478 (1967).

(7) W. T. Miller, Jr., *J. Amer. Chem. Soc.*, **82**, 3091 (1960), had probably synthesized perfluoroheptene-2; however, no attempt was made to identify it.

(8) R. N. Dresdner, F. N. Tlumac, and J. A. Young, *J. Org. Chem.*, **30**, 3524 (1965).

hexafluoropropene dimers[9] gave only two monobromides. No perfluorohexane was found in the product.



As was evident from the data in Table I, the formation of these products arose almost exclusively from the *trans* olefin **1**.

TABLE I

REACTION OF HEXAFLUOROPROPENE DIMER WITH BrF_3–Br_2

Structure	%[a] present before reaction	%[a] present after reaction
1	87.43	12.53
2	7.09	7.13
3	5.48	5.16
4	0	37.46
5	0	37.72

[a] Area measurement by gas chromatographic analysis.

The structures of the two perfluoro monobromides were assigned on the basis of the ^{19}F nmr results. The room temperature ^{19}F nmr data of structures **4** and **5** were given in Table II.

TABLE II

	4		5	
	ϕ	J	ϕ	J
$(CF_3)_2CF$–	72.2		69.4	
CF_3–	75.5		77.9	
CF_2–	98.2, 103.4	296	109.5, 114.5	283
	108.4, 113.7		117.4, 122.4	
CFBr–	142.1		137.7	
CF	180.8		171.5, 172.0	

The assignment of structure was based on chemical shifts, area measurements, and observed coupling patterns. The data are consistent with the conclusion that structurally related fluorines which are closest to the CFBr group in the above two compounds will be deshielded to the greatest extent. The deshielding effect of the perfluoroisopropyl group is likewise considered.

The high-resolution nmr spectrum of **4** shows complex multiplets for $(CF_3)_2CF$, CF_3CFBr, and $(CF_3)_2CF$ fluorines, while the CF_2 and CFBr nuclei appear as broad unresolved peaks. The $(CF_3)_2CF$ fluorines which give essentially one absorption at room temperature are seen as two distinct signals (71.7 and 79.8) at low temperature (−105°). The individual members of the AB quartet attributed to the CF_2 geminal fluorines are unaffected by variations in temperature. The chemical-shift difference, however, increases from 505 Hz at 24° to 568 Hz at −105°. Upfield shifts in the peak positions of the CFBr and $(CF_3)_2CF$ fluorines [CFBr, ϕ 145.0; $(CF_3)_2CF$, ϕ 181.4] occur with lowering of temperature. These observations reflect changes in conformer population. Studies from −105 to 80° indicate that at −105° interconversion between conformers has not been slowed sufficiently so that individual rotamers are observed.

The high-resolution room-temperature nmr spectrum of **5** shows the $(CF3)_2CF$ fluorines as an unsymmetrical multiplet. The CF_3CF_2 fluorines appear as a doublet of doublets (J = 6.6 Hz). The individual members of the AB quartet (chemical-shift difference = 340 Hz at 24°) due to the geminal CF_2 fluorines are broad as are the CFBr and CF fluorines. The latter shows doublet structure due to coupling with the adjacent CFBr. Spectra obtained at low temperature (−105°) show the following differences resulting from changes in conformer population. The isopropyl CF_3's are partially resolved (ϕ 69.4 and 70.0). The chemical-shift difference of the geminal CF_2 fluorines increases to 392 Hz. Both CFBr and $(CF_3)_2CF$ fluorines experience upfield shifts as the temperature is lowered [CFBr, 141.3; $(CF_3)_2CF$, 173.3 Hz]. As in the case of **4** no individual rotamers were observed.

The above results indicated that bromoperfluoro alkanes may be successfully prepared by the reaction of certain perfluoro alkenes with bromine trifluoride in bromine. In case of perfluoroheptene-1, the addition of BrF was stereospecific and yielded only the 2-bromo adduct. On the other hand, reactions involving additions to internal double bonds such as perfluoroheptene-2 and *trans*-perfluoro-4-methylpentene-2 (**1**) led to nearly equal amounts of the two possible adducts and thus proceeded with little selectivity. The apparent difference in reactivity between structures **1** and **2** and structures **2** and *cis*-perfluoroheptene-2 clearly resulted from the steric effect of the large perfluoroisopropyl group next to an internal double bond. This observation was further substantiated by the fact that the highly substituted double bonds of hexafluoropropene trimer[9] did not give BrF adducts under similar reaction conditions.

Experimental Section

The chromatographic preparative-scale separations for perfluoroheptenes and their bromides were performed on a Nester–Faust "Prepkro" unit using a column packed with 30% SF-96 on Chromosorb P (24 ft × 3/8 in.). The chromatographic preparative scale separations for hexafluoropropene dimers and their bromides were performed on a Wilkens Autoprep Model A 700 utilizing a column at 60° packed with 30% SE-30 on Chromosorb W (20 ft × 3/8 in.). The elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Infrared spectra were obtained with a Perkin-Elmer Model 137 double-beam spectrophotometer. The ^{19}F nmr spectra were obtained with a 60-MHz Varian DP-60 spectrometer. Spectra were calibrated by the side-band modulation technique using a Hewlett-Packard wide range oscillator. All ^{19}F chemical shifts were determined with $CFCl_3$ as an internal standard. Sample concentrations were approximately 20–40% by weight in $CFCl_3$. A Bendix time-of-flight mass spectrometer (Model 12-101) with source elements S14-107 was employed to record the mass spectra at 70 eV.

Reaction of Perfluoroheptene-1 with Bromine Trifluoride and Bromine.—Bromine trifluoride (0.06 mol) and bromine (0.12 mol) were placed in an ice-cooled flask equipped with a thermometer, a dropping funnel, a reflux condenser, and a stirrer. Perfluoroheptene-1[10] (0.143 mol) was added slowly to the BrF_3–Br_2 solution. The reaction was extremely exothermic. An ice bath was used to maintain the reaction temperature at 40–50°

(9) Synthesized according to W. J. Brehm, *et al.*, U. S. Patent 2,918,501 (1959).

(10) Synthesized according to J. D. LaZerte, L. J. Hals, T. S. Reid, and G. H. Smith, *J. Amer. Chem. Soc.*, **75**, 4525 (1953).

during the addition. After addition, stirring was continued for 1 hr at 25°. Excess BrF_3 and Br_2 were decomposed by washing with 10% aqueous $NaHSO_3$. The fluorocarbon layer was water washed and dried ($MgSO_4$). The crude product (89%) was fractionated by gas chromatography. The following peaks were collected and identified.

Perfluoro-*trans*-2-bromohexene-2 (9%): ^{19}F nmr CF_3C=C, ϕ 76.6, CF_3CF_2, 82.3, CF_2C=, 115.3, CF_3CF_2, 125.4, CF=, 143.1; ir ($CFCl_3$) 7.45 (s), 7.7–8.6, (vs), 8.82 and 8.95 (doublet, m), 9.98 (m), 10.6 (s), 10.9 (s), 12.65 (s), 13.48 (m), 13.9 (s), 14.3 (s), 14.55 (w), 14.9 μ (m); mass spectrum *m/e* (relative intensity) ion 343, 341 (6.5, 6.0) $C_6H_{10}Br^+$; 243, 241 (2.9, 2.5) $C_4F_6Br^+$; 231 (0.7) $C_5F_9^+$; 219 (0.7) $C_4F_7^+$; 193, 191 (5.2, 4.9) $C_3F_4Br^+$; 181, 179 (24.3, 20.0) $C_4F_7^+$ and $C_2F_4Br^+$; 169 (2.9) $C_3F_7^+$; 150 (0.9) $C_3F_6^+$; 131, 129 (30.9, 8.8) $C_3F_5^+$ and CF_2Br^+; 119 (42.1) $C_2F_5^+$; 112 (1.9) $C_3F_4^+$; 100 (17.4) $C_2F_4^+$; 93 (14.8) $C_3F_3^+$; 81,79 (4.7, 4.3) Br^+; 69 (100) CF_3^+; 50 (19.8) CF_2^+; 31 (80.0) CF^+.

Perfluoro-*trans*-2-bromo-heptene-2 (4%): ^{19}F nmr CF_3C=C, ϕ 76.6, CF_3CF_2 82.2, CF_2C=, 114.6, CF_2CF_2C=, 121.7, CF_3CF_2, 127.7, CF=, 142.5; ir ($CFCl_3$) 7.4 (m), 7.6–8.5 (vs), 8.75 (s), 10.2 (w), 10.45 (w), 10.7 (m), 10.82 (m), 13.45 (m), 14.1 (m), 14.6 (m), 14.7 μ (sh); mass spectrum *m/e* (relative intensity) ion 393, 391 (7.0, 6.5) $C_7F_{12}Br^+$; 374, 372 (0.7, 0.6), $C_7F_{11}Br^+$; 293, 291 (1.5, 1.1) $C_5F_8Br^+$; 243, 241 (0.9, 0.8) $C_4F_6Br^+$; 231, 229 (3.4, 3.0) $C_3F_6Br^+$; 193, 191 (1.5, 1.3) $C_3F_4Br^+$; 181, 179 (31.6, 30.2) $C_2F_4Br^+$; 169 (18.9) $C_3F_7^+$; 162, 160 (2.6, 1.6) $C_4F_6^+$ and $C_2F_3Br^+$; 150 (1.3) $C_3F_6^+$; 131, 129 (55.2, 13.2) C_3F_5 and CF_2Br^+; 119 (36.3) $C_2F_5^+$; 112 (3.2) $C_3F_4^+$; 100 (43.9) $C_2F_4^+$; 93 (20.8) $C_3F_3^+$; 81, 79 (8.9, 3.9) $C_2F_3^+$ and Br^+; 69 (100) CF_3^+; 50 (20.5) CF_2^+; 31 (91.0) CF^+.

Perfluoro-2-bromoheptane (87%): bp 114–116°, $n^{20}D$ 1.3036; ^{19}F nmr CF_3CFBr, ϕ 76.0, CF_3CF_2, 81.8, CF_2CFBr, 113.9, CF_2CF_2CFBr, 119.5, $CF_3CF_2CF_2$, 123.1, CF_3CF_2, 127.1, CFBr, 141.2; ir 7.4 (m), 7.6–9.0 (s), 9.71 (m), 9.82 and 9.9 (doublet, m), 10.2 (m), 10.6 (m), 10.92 (s), 11.3 (m), 11.6 (w), 12.1 (w), 12.45 (m), 12.57 (m), 12.92 (m), 13.1 (w), 13.4 (s), 13.62 (s), 14.1 (s), 14.7 μ (s); mass spectrum *m/e* (relative intensity) ion 450, 448 (4.5, 4.0) $C_7F_{15}Br^+$ (parent ion); 431, 429 (0.9, 0.8) $C_7F_{14}Br^+$; 231, 229 (5.0, 4.3) $C_3F_6Br^+$; 219 (8.3) $C_4F_3^+$; 193, 191 (6.2, 5.7) $C_3F_4Br^+$; 181, 179 (45.2, 37.6) $C_2F_4Br^+$; 169 (13.1) $C_3F_7^+$; 162, 160 (3.6 1.9) $C_2F_3Br^+$; 150 (3.8) $C_3F_6^+$; 131, 129 (78.5, 14.3) $C_3F_5^+$ and CF_2Br^+; 119 (51.2) $C_2F_5^+$; 112 (4.3) $C_3F_4^+$; 100 (51.3) $C_2F_4^+$; 93 (21.4) $C_3F_3^+$; 81, 79 (9.5, 4.8) $C_2F_3^+$ and Br^+; 69 (100) CF_3^+; 50 (10.7) CF_2^+; 31 (73.8) CF^+.

Preparation of Perfluoroheptene-2.[7]—Perfluoroheptene-1 (100 g) was heated under reflux (80–76°) with powdered cesium fluoride (3 g) for 10 hr with stirring. The reaction mixture was washed with water, dried ($MgSO_4$), and distilled giving a fraction (83 g) which boiled at 75.5–76.5°. Vpc collections were carried out at 20°. Area determinations indicated the presence of perfluoro-*trans*-heptene-2 (74%), *cis* heptene-2 (16%), and unreacted perfluoroheptene-1 (7%).

Perfluoro-*trans*-heptene-2: ir 6.0 (C=C, w), 7.15 (m), 7.45 (s), 7.7–8.9 (vs), 9.5 (m), 9.78 (m), 10.15 (m), 10.65 (w), 10.8 (w), 11.2 (s), 12.1 (m), 12.3 (m), 12.5 (m), 13.39 and 13.45 (doublet, s), 13.8 (s), 14.0 (w), 14.4 (m), 14.7 μ (w); ^{19}F nmr CF_3C=C, ϕ 70.0, CF_3CF_2, 82.0, CF_2C=C, 119.2, CF_2CF_2C=C, 125.3, CF_3CF_2, 127.2, CF=CF, 158.3.

Perfluoro-*cis*-heptene-2: ir ($CFCl_3$) 5.9 (C=C, m), 7.5 (s), 7.9–8.7 (vs), 8.9 (s), 9.1 (m), 9.4 (m), 9.6 (m), 9.8 (w), 10.2 (m), 10.68 (m), 10.9 (w), 11.3 (w), 12.5 (s), 13.45 (m), 13.68 and 13.8 μ (doublet, s); ^{19}F nmr CF_3C=C, ϕ 66.3, CF_3CF_2, 81.9, CF_2C=C, 116.9, CF_2CF_2C=C, 124.1, CF_3CF_2, 127.1, CF_2CF=, 137.7, CF_3CF=, 141.0.

Reaction of Perfluoroheptene-2 with Bromine Trifluoride and Bromine.—A mixture of *trans*- (82%) and *cis*- (18%) perfluoroheptenes-2 (35 g, 0.1 mol) was allowed to react with a solution of BrF_3 (5.5 g, 0.04 mol) and Br_2 (12.8 g, 0.08 mol) as described previously. The crude product contained about 10 g of the unreacted perfluoroheptenes-2 (*trans* 80% and *cis* 20%) and 26 g (58%) of a colorless liquid. Vpc analysis of the colorless liquid at 130° showed one large peak with a shoulder. The peak and shoulder were collected together and analyzed by ^{19}F nmr. Peak intensity ratios indicated that there were two components present in 50:50 ratio. They were identified as perfluoro-2 bromoheptane and perfluoro-3-bromoheptane. The individual peaks in the ^{19}F nmr spectra were assigned as follows: CF_3CFBr, ϕ 76.0 (2-bromo), CF_3CF_2CFBr, 78.8 (3-bromo), CF_3CF_2, 81.8 (2-bromo + 3-bromo), CF_2CFBr, 113.4 (3-bromo), CF_2CFBr, 113.9 (2-bromo), CF_3CF_2CFBr, 117.0 (3-bromo), CF_2CF_2CFBr, 119.5 (2-bromo), $CF_3CF_2CF_2$, 119.9 (3-bromo), $CF_3CF_2CF_2$, 123.1 (2-bromo), CF_3CF_2, 127.0 (2-bromo + 3-bromo), CFBr, 139.4 (3-bromo), CFBr, 141.1 (2-bromo). The infrared spectrum of the mixture shows considerable band overlapping and the presence of the 3-bromo isomer could not be definitely established by this method. The mass spectrum of the mixture, except for peak intensities, was very similar to that obtained for the 2-bromo isomer with the $C_7F_{15}Br^+$ fragment being the highest fragment observed in the spectrum.

Reaction of Hexafluoropropene Dimer with Bromine Trifluoride in Bromine.—Hexafluoropropene dimer[9] C_6F_{12} (300 g, 1 mol) was added during 45 min to an ice-cooled solution of BrF_3 (46 g, 0.33 mol) in Br_2 (55 g, 0.33 mol). The product (340 g) contained the three isomers of C_6F_{12} (**1**, **2**, **3**), in different ratios (see text, Table I) and the two isomers of $C_6F_{13}Br$ (**4**, **5**). The monobromides were separated from the dimers by fractional distillation. The mixed bromides have the following physical constants: bp 97–100°, d^{21} 1.9220; $n^{20}D$ 1.3049; calcd molar refractivity (MR) 37.5, found 39.1. The two bromides were further fractionated by gas chromatography and analyzed by mass spectroscopy and ^{19}F nmr.

4: mass spectrum *m/e* (relative intensity) ion 400, 398 (0.7, 0.6) $C_6F_{13}Br^+$ (parent ion); 381, 379 (0.3, 0.2) $C_6F_{12}Br^+$; 293, 291 (0.8, 0.7) $C_5F_8Br^+$; 243, 241 (0.1, 0.2) $C_4F_6Br^+$; 231, 229 (1.2, 0.7) 193, 191 (0.7, 0.3) $C_3F_4Br^+$ and $C_5F_7^+$; 181 (6.3) $C_4F_7^+$; 169 (0.2) $C_3F_7^+$; 162 (1.2) $C_2F_3Br^+$ and $C_4F_6^+$; 160 (0.9) $C_2F_3Br^+$; 131, 129 (8.8, 1.8) CF_2Br^+ and $C_3F_5^+$; 124 (0.4) $C_4F_4^+$; 119 (0.9) $C_2F_5^+$; 112 (1.2) $C_3F_4^+$; 100 (4.7) $C_2F_4^+$; 93 (5.1) $C_3F_3^+$; 81, 79 (2.6, 1.6) Br^+; 69 (100.0) CF_3^+; 50 (2.6) CF_2^+; 31 (17.6) CF^+; ir 7.6–8.5 (vs), 8.75 (s), 8.92 (s), 10.2 (s), 10.9 (s), 12.3 (s), 12.7 (m), 13.2 (s), 13.6 (s), 14.0 (w), 14.2 (s), 14.4 μ (s).

Anal. Calcd for $C_6F_{13}Br$: C, 18.06; F, 61.91; Br, 20.03. Found: C, 18.20; F, 61.66; Br, 20.13.

5: mass spectrum *m/e* (relative intensity) ion 400, 398 (0.1, 0.2) $C_6F_{13}Br^+$ (parent ion); 381, 379 (0.1, 0.1) $C_6F_{12}Br^+$; 293, 291 (0.3, 0.8) $C_5F_8Br^+$; 281, 279 (2.0, 1.7) $C_4F_8Br^+$; 243, 241 (0.1, 0.4) $C_4F_6Br^+$; 231, 229 (1.4, 0.8) 193, 191 (0.9, 0.3) $C_3F_4Br^+$ and $C_5F_7^+$; 181 (2.6) $C_4F_7^+$; 169 (0.4) $C_3F_7^+$; 162 (0.5) $C_2F_3Br^+$ and $C_4F_6^+$; 160 (0.3) $C_2F_3Br^+$; 131, 129 (7.8, 3.3) CF_2Br^+ and $C_3F_5^+$; 124 (0.4) $C_4F_4^+$; 119 (2.1) $C_2F_5^+$; 112 (0.9) $C_3F_4^+$; 100 (1.9) $C_2F_4^+$; 93 (6.1) $C_3F_3^+$; 81, 79 (1.4, 1.1) Br^+; 69 (100.0) CF_3^+; 50 (2.6) CF_2^+; 31 (8.5) CF^+; ir 7.6–8.5 (vs), 8.72 (s), 8.99 (s), 9.13 (s), 10.18 (s), 11.2 (s), 11.5 (m), 12.2 (m), 12.38 (m), 13.2 (m), 13.6 (s), 13.97 (s), and 14.3 μ (s).

Anal. Calcd for $C_6F_{13}Br$: C, 18.06; F, 61.91; Br, 20.03. Found: C, 18.07; F, 61.71; Br, 20.26.

Registry No.—Bromine trifluoride, 7787-71-5; perfluoroheptene-1, 355-63-5; perfluoro-*trans*-2-bromohexene-2, 24010-45-5; perfluoro-*trans*-2-bromoheptene-2, 24057-16-7; perfluoro-2-bromoheptane, 24010-68-2; perfluoro-*trans*-heptene-2, 24010-46-6; perfluoro-*cis*-heptene-2, 24010-47-7; **4**, 24010-48-8; **5**, 24057-17-8.

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Directing a Chlorination Reaction

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We have been able to modify the course of the reaction between chlorine and hexane by carrying out the reaction in a "molecular sieve." When hexane,

absorbed at 150° in a synthetic zeolite, a Linde 13X Molecular Sieve, is treated with chlorine, the ratio of secondary to primary chlorination rate constants [R (calculated on an H-atom basis) = k_s/k_p] is 1.1–1.9 (the conversion of hexane being 1.0 and 8.3%, respectively). Pretreatment of the sieve with chlorine lowers the R value further, even though the chlorine is desorbed before absorbing the hexane.

Conversion of hexane, %	R
0.71–1.7	0.3–0.8
11.8	1.9
52	2.2

At 150°, the homogeneous gas-phase reaction between chlorine and hexane yielded an R value of 2.7–3.7 (1–42% conversion, 0.5–9-sec contact time, and a molar ratio range of chlorine to hexane of 1–7). A small quantity of dichlorinated products was also obtained (*e.g.*, less than 1% in the product at 15% conversion of hexane), but these were not detected for the sieve reactions. Values for R of 2.8–6.0 in the homogeneous gas phase have been reported for the same or similar reactions.[1-3]

The pore size of the sieve is critical. Openings of 5 Å are too small to permit recovery of the product from the sieve. Openings of 13 Å are satisfactory. Openings of 10 Å appear to be borderline in value.

The increase in the value of R as the conversion is increased may be attributable to desorption of hexane from the sieve followed by reaction in the homogeneous phase. From desorption experiments with pure hexane, we have estimated that a maximum of 10% of the hexane in the sieve could have reacted in the vapor phase when the total conversion exceeded 15%. Under these circumstances, the molar ratio of chlorine to hexane in the vapor phase would be greater than 100:1 so that reaction would be rapid.

Reviewers raised the question as to whether secondary chlorides which were formed may have been dehydrohalogenated selectively to give the low R values. While no complete material balance was obtained, the following experimental facts make such a possibility remote. (1) In the normal sieve reactions, no alkenes were found. The only by-product detected was hexachlorobenzene in very small quantities. The overall time of the sieve reactions was 1–4 min. 1-Chlorohexane, deposited on the 13X sieve at 150°, left there for 80 min, and removed with steam at 150°, yielded a mixture of alkenes and 1-chlorohexane. (2) When 5A sieves were used under normal reaction conditions, product recovery was not possible as mentioned above. When the chlorination reaction was continued for extended periods of time over 5A sieves without the introduction of steam, a mixture of chlorohexanes was collected with an R ratio of 3.7–3.9, probably as a result of gas-phase chlorination. If selective dehydrohalogenation of secondary chlorohexanes occurred over sieves, the R value would be abnormally low. (3) If dehydrohalogenation were the cause of low R values, the R value would not be the increasing function of conversion noted in the text.

(1) I. Gabila, J. M. Tedder, and J. C. Walton, *J. Chem. Soc., B*, **7**, 604 (1966).

(2) J. M. Tedder, and R. A. Watson, *Trans. Faraday Soc.*, **62**, 1215 (1961).

(3) G. C. Fettes and J. H. Knox, *Progr. Reaction Kinetics*, **2**, 1 (1964).

Experimental Section

Analysis.—The products of the reaction were analyzed by vapor phase chromatography using a 14-ft column containing 20% Carbowax on Gas-Chrom P (column temperature of 200°, feed block at 275°, with a thermal detector). The concentrations were estimated from the recorder peak heights. Pure materials and their mixtures were used to calibrate the vpc instrument, but only one secondary monochloride was available in pure form. Occasional confirmation of the identity of the individual components was made *via* nmr. A single peak on the chromatograph included all of the secondary monochlorohalides. Any component which was present in an amount greater than 0.5% would have been detected by the chromatograph.

Materials.—Linde 5X, 10X, and 13X Molecular Sieves (Union Carbide Corp) with 5-, 10-, and 13-Å pores respectively, were used directly as received ($^1/_{16}$-in. pellets). n-Hexane was Matheson Coleman and Bell Spectroquality; Cl_2 was 99.965% minimum purity with less than 3 ppm of water; HCl was 99.0% minimum purity, dried over H_2SO_4 before use; the nitrogen has less than 15 ppm of water and less than 0.002% oxygen.

Absorption and Desorption of Hexane on the Sieves.—The sieves were placed in a 30-in.-long, 25-mm-i.d. Pyrex tube and dried at 350–370° for 2 hr and under a stream of nitrogen. Mixed vapors of hexane and nitrogen were passed through the bed which was held at 150°. The absorption data were obtained gravimetrically. For desorption studies, pure nitrogen was passed through the bed containing the absorbed hexane. The effluent from the Pyrex tube was trapped at 0 and −76° in a series of traps. The absorption data were in reasonable agreement with those of Allen.[4]

Reaction of n-Hexane and Chlorine in the Molecular Sieves.—The same apparatus was used as for absorption studies with the additional precaution of eliminating free space before the sieve bed by the insertion of a close-fitting sealed Pyrex tube. Water was removed from 65 to 72 g of sieves at 450–480°. Hexane was deposited on the sieve at 150° by absorption from a stream of nitrogen. A mixture of chlorine and nitrogen was passed over the sieve for a predetermined length of time (experimental range of 1–4 min). The reactor was swept briefly with nitrogen, and the hydrocarbon was displaced from the sieve with water vapor mixed with enough nitrogen to prevent a negative pressure from forming. The time delay between the introduction of the various streams was less than 3 sec. When the water was introduced, the effluent from the reactor was led through wet and Dry Ice traps in series. After separating and discarding the aqueous phase, the excess chlorine in the trapped liquid was allowed to bleed into the atmosphere at 25° before analyzing the product. Essentially all of the chlorinated product was trapped at 0°. Fresh sieves were used for each experiment to avoid the problem of reaction between HCl and the sieves, which reaction was shown to occur slowly.

Homogeneous Gas-Phase Reaction of Chlorine and Hexane.—A Pyrex tube of 25-cc free volume served as the reactor. Mixed preheated streams of nitrogen, hexane, and chlorine were fed to the reactor at 150°. The off-gases were trapped and analyzed as described above.

Registry No.—Hexane, 110-54-3.

Acknowledgment.—Analyses, other than vpc, were performed by J. H. Turney, R. Coffee, and J. C. Randall. A. L. Caviness assisted with the experimental work.

(4) C. L. Allen, "The Kinetics of Adsorption of Pure Hydrocarbons by Synthetic Zeolites," Thesis, Department of Chemistry, Clarkson College of Technology, Oct 29, 1964.

Perfluoro-*t*-butyl Alcohol and Its Esters

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Perfluoroalkylcarbinols are especially interesting because of the large electronegativity of the fluorine

atom and consequently the large inductive effects of the perfluoroalkyl group or groups.

The acidic properties of fluorine-containing alcohols and the synthesis of perfluoro-*t*-butyl alcohols have been summarized by Dyatkin, Mochalina, and Knunyants[1] and by Filler and Schure.[2] Dyatkin, *et al.*, obtained perfluoro-*t*-butyl alcohol from perfluoro-2-nitroso-2-methylpropane by oxidation to the nitrite and hydrolysis. Filler and Schure treated

$$(CF_3)_3CNO \longrightarrow (CF_3)_3CONO \longrightarrow (CF_3)_3COH$$

CCl_3Li with hexafluoroacetone. The trichloro compound was then treated with antimony pentafluoride to form the perfluoro-*t*-butyl alcohol.

$$(CF_3)_2C{=}O + CCl_3Li \longrightarrow (CF_3)_2(CCl_3)COH \xrightarrow{SbF_5} (CF_3)_3COH$$

The method used in our laboratory was to use perfluoroisobutene oxide as starting material. A good

$$(CF_3)_2C\text{---}CF_2 + HF + SbF_5 \longrightarrow (CF_3)_3COH$$
$$\qquad\quad \backslash\, /$$
$$\qquad\quad\ O$$

yield of the alcohol is obtained and only catalytic quantities of antimony pentafluoride are required. Preparation of the oxide, the alcohol, and esters of the alcohol are described in the Experimental Section.

To obtain an estimate of the inductive effects, pseudo-first-order hydrolysis rates at pH 11 were determined for the perfluoro-*t*-butyl acetate and trifluoroacetate. These were compared with those for 1,1,1-trifluoroethyl acetate and trifluoroacetate and also those for ethyl trifluoroacetate and ethyl acetate. Table I shows the results obtained.

TABLE I

FIRST-ORDER HYDROLYSIS RATES OF FLUORO ESTERS AT CONTROLLED (CONSTANT) pH

	$t_{1/2}$, min,	k, min^{-1} × 10^4		
	5°	5°	15°	25°
$CH_3CH_2OOCCH_3$ (1)				24
$CH_3CH_2OOCCF_3$ (2)	<1	>6000		>6000
$CF_3CH_2OOCCH_3$ (3)	346	20	81	150
$CF_3CH_2OOCCF_3$ (4)	<1	>6000		>6000
$(CF_3)_3COOCCH_3$ (5)	23.6	294	1410	1962
$(CF_3)_3COOCCF_3$ (6)	3.2	2160		>6000

Discussion of Results

As expected, the inductive effects of the trifluoroacetate group are very pronounced under alkaline hydrolysis conditions. The trifluoromethyl group also shows an inductive effect even though it is shielded by an oxygen and a methylene group (**3**). The inductive effects of the *t*-butyl group (**5**) are over fourteen times that of the trifluoroethyl group, indicating that inductive effects are appreciably more important than steric effects. However, steric effects can be seen when **4** and **6** are compared; the perfluoro-*t*-butyl trifluoroacetate has a half-life over three times as great as the trifluoroethyl trifluoroacetate. The steric effects of the perfluoro-*t*-butyl group do extend in a measurable degree to the carbonyl group.

(1) B. L. Dyatkin, E. P. Mochalina and I. L. Knunyants, *Tetrahedron*, **21**, 2991 (1965).

(2) R. Filler and R. M. Schure, *J. Org. Chem.*, **32**, 1217 (1967).

Acid hydrolysis of the perfluoro-*t*-butyl acetate (**5**) was found to be very slow. Thus, after 94 hr only 10% was hydrolyzed (0.1 *N* HCl in aqueous acetone). In addition to the inductive effects causing a partial positive charge at the alkyl oxygen, site of cationic attack, the steric effects of the *t*-butyl group appear to be significant.

Experimental Section

Preparation of Perfluoroisobutylene Oxide.—*Caution!* *i*-C_4F_8 is very toxic, 0.5 ppm. At 0–5° 277 g of 75% *i*-C_4F_8 (1.05 mol) was mixed with 220 ml of 30% H_2O_2, 55 ml of acetone, and 30 g of $Na_2HPO_4 \cdot 7H_2O$. While the mixture was stirring, 200 ml of H_2O containing 56 g of Na_2CO_3 was added dropwise during 85 min. Stirring was continued for 3 hr after the addition of carbonate; then the low boiling fluorocarbons were distilled out into Dry Ice cooled traps; there was 167 g of product. Ir spectroscopy showed the oxide absorption at 6.66 μ. Nmr spectroscopy indicated the oxide structure: CF_3, ϕ^* 69.6; CF_2, ϕ^* 109.2. The molecular weight utilizing a density balance was 219, theoretically 216. The boiling point of a purified fraction is 3°.

Anal. Calcd for C_4F_8O: C, 22.2; F, 70.4. Found: C, 22.1; F, 70.0.

Preparation of Perfluoro-*t*-butyl Alcohol.—To 20 g (1.0 mol) of anhydrous hydrogen fluoride and 5 g of antimony pentafluoride in a 300-ml stainless steel autoclave was charged 35 g of crude perfluoroisobutylene oxide. The mixture was agitated in an Aminco rocking mechanism at 100° for 16 hr. The product was then distilled out and passed through a steel tube (1-in. diam × 30 in. long) containing sodium fluoride pellets to remove hydrogen fluoride; 21 g of perfluoro-*t*-butyl alcohol was obtained, bp 48°. The characteristic ir absorption for the hydroxy group is at 2.74 μ. The nmr spectrum showed the tertiary alcohol structure: CF_3, ϕ^* 74.95; OH, τ 6.64.

Anal. Calcd for C_4F_9OH: C, 20.3; F, 72.15. Found: C, 20.5; F, 72.3.

Preparation of Esters.—Compounds $CF_3CH_2OOCCF_3$, $CF_3CH_2OOCCH_3$, and $CH_3CH_2OOCCF_3$ were prepared by known methods and their ir spectra compared favorably with spectra of authentic samples.

$(CF_3)_3COOCCH_3$.—To 1.90 g (0.02 mol) of 2-methylpyridine was added dropwise at 0–5° 4.72 g (0.02 mol) of perfluoro-*t*-butyl alcohol; then 4.2 g (0.02 mol) of acetic anhydride was added while stirring magnetically. Stirring was continued at room temperature for 48 hr. Distillation of the mixture gave 3.1 g, bp 81–83°, which was further purified by being passed through Drierite *in vacuo*. The ir spectrum showed the ester absorption at 5.43 μ.

Anal. Calcd for $C_6F_9H_3O_2$: C, 25.9; F, 61.5. Found: C, 26.2; F, 60.6.

$(CF_3)_3COOCCF_3$.—To 2.1 g (0.02 mol) of 2-methylpyridine cooled to 5°, 4.2 g (0.02 mol) of trifluoroacetic anhydride was added dropwise with stirring; then 4.72 g (0.02 mol) of perfluoro-*t*-butyl alcohol was added slowly. Stirring was continued at room temperature for 48 hr. Distillation of this mixture gave a main fraction, bp 57–58° (740 mm). The ir showed good material; absorption for the carbonyl was found at 5.40 μ. The material failed to give satisfactory analytical data.

Anal. Calcd for $C_6F_{12}O_2$: C, 21.9; F, 68.6. Found: C, 20.8; F, 65.6.

Hydrolysis Data.—Rates of base hydrolysis are usually determined by periodically removing samples of a reaction mixture, quenching the reaction with a known amount of acid, and back-titrating the excess acid to determine the base content of the original sample. This procedure requires a complete titration for each point on the hydrolysis curve and its accuracy is often limited because the small amount of acid formed by the hydrolysis reaction is calculated from the difference of two large quantities. The procedure used in this work is based on the maintenance of a constant pH in the reaction mixture by the controlled addition of standard base. The amount of base added at any time is then a direct measure of the acid formed by the hydrolysis reaction. Under constant pH conditions, the reaction should follow first-order kinetics and the plot of log concentration of ester *vs.* reciprocal time should be linear.

Rates of hydrolysis are obtained at constant pH by use of a Radio-meter Type TTT-1 automatic titrator controlling a motor-driven Gilmont micropipet. Reactions are carried out in 50 ml

of 1:1 acetone–water solution contained in a 100-ml titration vessel. Before addition of the sample, the controller is set at pH 11, causing base to be delivered from the micropipet until this pH reading is reached. (In this partly nonaqueous solvent, a pH reading of 11 does not necessarily correspond to the hydroxyl ion concentration of 10^{-3}.) The amount of sample is determined from the total base requirement of the complete reaction; at pH 11 the reverse reaction should be negligible. As the acid is produced by hydrolysis of the ester, the pH of the solution tends to decrease, and the controller delivers more base from the micropipet to maintain the pH reading at 11. The buret reading at any time is a direct measure of the amount of acid produced by hydrolysis and the hydrolysis curve can be obtained by plotting buret reading *vs.* time.

First-order rate constants are obtained from the slope of the plot of log of fraction of ester remaining *vs.* reciprocal time. The ester remaining at any time is proportional to the total base required for the completed reaction minus the base already added at that time.

$$\log\left(\frac{V_{\text{total}} - V_x}{V_{\text{total}}}\right) = \frac{1}{kt_x}$$

Registry No.—Perfluoro-*t*-butyl alcohol, 2378-02-1; perfluoroisobutylene oxide, 707-13-1; $(CF_3)_3COOCCH_3$, 24165-09-1; $(CF_3)_3COOCCF_3$, 24165-10-4.

N-Bromination of Amides, Imides, and Sulfonamides with Acetyl Hypobromite

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The N-bromination of amides and imides has been accomplished by a number of workers. In most cases, successful N-bromination of amides and imides has been done by using bromine in an aqueous alkaline medium.[1] However, several investigators have devised N-brominating methods for specific compounds. Park, *et al.*,[2] used bromine with silver oxide in trifluoroacetic acid for perfluoroamides, while Neale, *et al.*,[3] used *t*-butyl hypobromite for sterically hindered amides such as N-*t*-butylpentanoamide. Also, Waugh and Waugh[4] patented a procedure to N-brominate amides which used bromine with sodium bromate in aqueous sulfuric acid.

We have discovered a new reaction in which acetyl hypobromite in carbon tetrachloride solution N-monobrominates not only imides but also unsubstituted amides, sterically hindered N-*t*-butylamides, perfluoroamides, and N-alkylsulfonamides in excellent yields. In similar fashion unsubstituted amides and sulfonamides undergo N,N-dibromination in excellent yield upon treatment with acetyl hypobromite. Numerous N,N-dibromosulfonamides have been previously prepared; however, to our knowledge N,N-dibromoamides have not yet been isolated. Examples of the N-monobromination and N,N-dibromination reaction are given using N-*t*-butyl-4-nitrobenzamide (1) and 4-nitrobenzamide (2).

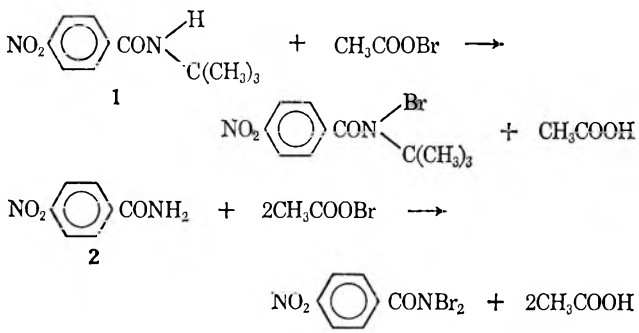
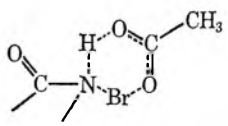


Table I gives the per cent yield of product before any recrystallization attempts were made and also gives the percentage of theoretically possible active bromine found.

The advantage of using acetyl hypobromite for N-bromination of amides and imides, in addition to the nearly quantitative yield of product obtained, is the ease with which the reactions can be carried out. A mixture of the reagent to be brominated and the carbon tetrachloride solution of acetyl hypobromite is stirred at room temperature from 15–60 min. The carbon tetrachloride solvent, the excess acetyl hypobromite, and the acetic acid by-product are evaporated at reduced pressure leaving essentially quantitative yields of very pure product. The reactions were monitored visually. N,N-Dibromo and N-alkyl-N-bromo products dissolved in the carbon tetrachloride solvent while N-bromoimides and monobromoamides settled to the bottom of the flask. Unreacted imides and amides usually floated on top of the carbon tetrachloride solvent.

A homogeneous reaction was performed using 0.0128 mmol of succinimide and 0.0140 mmol of acetyl hypobromite in 50 ml of methylene chloride. An attempt to follow the reaction by uv methods failed since the reaction was too fast. The reaction for N-bromination of amides and imides by acetyl hypobromite possibly occurs through a six-membered cyclic intermediate (or transition state).



Since the N-bromination of amides and imides with acetyl hypobromite worked so well an N-iodination of succinimide was attempted using acetyl hypoiodite. A stable solution of acetyl hypoiodite could not be prepared so the acetyl hypoiodite was prepared in an acetone solution containing succinimide which was to be iodinated. A mixture of succinimide, silver acetate, iodine, and acetone was stirred at 0° for 30 min, giving, after filtration and evaporation of the solvent, N-iodosuccinimide in 94% yield (active iodine was 98% of theory). N-Iodination of amides and imides with acetyl hypoiodite will be the topic of a future paper.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and were uncorrected. The carbon tetrachloride was distilled over calcium chloride. Bromine analyses were done by dissolving

(1) (a) F. Lengeld and J. Stieglitz, *J. Amer. Chem. Soc.*, **15**, 215 (1893). (b) F. D. Chattaway, *ibid.*, **87**, 145 (1905). (c) T. Seliwanow, *Ber.*, **26**, 423 (1893); Z. Foldi, *ibid.*, **63**, 2257 (1930). (d) H. Blitz and K. Slotta, *J. Prakt. Chem.*, **113**, 233 (1926).

(2) J. D. Park, H. J. Gerjovich, W. R. Lyean, and J. R. Lacher, *J. Amer. Chem. Soc.* **74**, 2189 (1952).

(3) R. S. Neale, N. L. Marcus, and R. G. Schepers, *ibid.*, **88**, 3051 (1966).

(4) T. D. Waugh and R. C. Waugh, U. S. Patent 2,971,960 (Feb 1961).

TABLE I

	Yield, %	Active bromine, % of theory	Mp, °C Obsd (crude)	Mp, °C Lit.
N-Bromo derivative of				
succinimide	98	95	168–169 dec	178 dec[a]
phthalimide	99	95	201–203 dec	206–207 dec[b]
N-methyl-4-nitrobenzamide	99	99	113–115 dec	
N-*t*-butyl-4-nitrobenzamide	99	97	131–134 dec	
4-nitrobenzamide	99	95	229–231 dec	192–202[c]
trifluoroacetamide	85	99	52–54 dec	62[d]
benzamide	98	94	126–128 dec	129–131dec[c]
N-methyl-4-toluenesulfonamide	101	98	106–107 dec	113 dec[a]
N,N-Dibromo derivative of				
4-nitrobenzamide	99	100	138–139 dec	
4-toluenesulfonamide	101	99	95–97 dec	104[a]

[a] Reference 1a. [b] Reference 4. [c] Reference b. [d] Reference 2.

the active-bromine compound in acetone, adding an equal volume of a 50:50 mixture of acetic acid and water plus an excess of potassium iodide and titrating for the released iodine with standard thiosulfate solution.

Acetyl Hypobromite.[5]—A mixture of silver acetate (5.6 g, 0.033 mol) and 150 ml of carbon tetrachloride was placed in a 500-ml round-bottom flask covered with aluminum foil. To the stirred mixture a carbon tetrachloride solution of bromine (2.15 *M*, 0.032 mol) was added dropwise over a period of 10 min as the reaction temperature was maintained at $-10 \pm 5°$. The mixture was stirred for an additional 10 min and then filtered. The carbon tetrachloride solution was diluted to 200 ml (0.136 *M*, 0.027 mol). All other acetyl hypobromite solutions were prepared in a similar manner. Solutions of acetyl hypobromite were stable up to four weeks when stored in the dark at -10 to $-15°$ temps. Solutions that were exposed to ordinary light at room temperature showed no activity after 8 hr. No problems were observed owing to rapid decomposition of the acetyl hypobromite.

N-Bromo-N-*t*-butyl-4-nitrobenzamide.—A mixture of N-*t*-butyl-4-nitrobenzamide (0.119 g, 0.5360 mmol) and 8 ml of acetyl hypobromite solution (0.108 *M*, 0.8061 mmol) in carbon tetrachloride was stirred at ambient temperature for 15 min in a 25-ml round-bottom flask. The flask was covered with aluminum foil to protect the product from light. The solution was evaporated at reduced pressure giving 0.1586 g of product, mp 136–137° (99% yield, active bromine was 97% of theory).

The product was recrystallized from an acetone–water mixture, giving an analytically pure material, mp 137–138° dec, ir 6.06 μ (Nujol mull) with no NH peak, uv 268 mμ (dioxane).

Anal. Calcd for $C_{11}H_{13}N_2O_3Br$: Br, 26.53. Found: Br, 26.34.

N,N-Dibromo-4-nitrobenzamide.—A mixture of 4-nitrobenzamide (0.173 g, 1.038 mmol) and 20 ml of acetyl hypobromite (0.124 M, 2.48 mmol) in carbon tetrachloride was stirred at ambient temperature for 75 min in a 50-ml round-bottom flask. The flask was covered with aluminum foil. The solution was evaporated at reduced pressure giving 0.332 g of analytically pure material, mp 138–139° dec (99% yield, active bromine was 99.7% of theory), ir 5.97 μ (Nujol mull) with no NH peak, uv 291 mμ (dioxane).

Anal. Calcd for $C_7H_4N_2O_3Br_2$: Br, 49.33. Found: Br, 49.18.

N-Bromobenzamide.—A mixture of benzamide (0.145 g, 1.20 mmol and 10 ml of acetyl hypobromite (0.126 M, 1.26 mmol) was stirred in the dark in a 25-ml round-bottom flask for 60 min at ambient temperatures. The mixture was evaporated at reduced pressure leaving 0.235 g of product, mp 126—128° dec (lit.[6] mp 129–131° dec) (98% yield, active bromine was 95% of theory).

N-Bromo-N-methyl-4-nitrobenzamide.—The N-methyl-4-nitrobenzamide was N-brominated in manner previously described in the N-*t*-butylamide. The N-bromo product was recrystallized from an acetone–water mixture, giving analytically pure material, mp 114–115° dec, ir 6.05 μ (Nujol mull) with no NH peak, uv 268 mμ (dioxane).

Anal. Calcd for $C_8H_7N_2O_3Br$: Br, 30.84. Found: Br, 30.53.

N-Iodosuccinimide.—A mixture of succinimide (0.166 g, 1.67 mmol), silver acetate (0.646 g, 3.87 mmol), and 10 ml of acetone was placed in a 50-ml round-bottom flask covered with aluminum foil. The flask was cooled in an ice bath and a solution of iodine (0.468 g, 1.84 mmol) in 15 ml of acetone was dropped in over a 5-min period. Stirring was continued for an additional 10 min. The mixture was filtered; the acetone solution was evaporated leaving 0.353 g (94% yield, active iodine was 96% of theory) of material, mp 191–193° dec (lit.[7] mp 201° dec).

Registry No.—Acetyl hypobromite, 4254-22-2; N-bromo-N-*t*-butyl-4-nitrobenzamide, 24472-09-1; N,N-dibromo-4-nitrobenzamide, 24472-10-4; N-bromo-N-methyl-4-nitrobenzamide, 24472-11-5.

Acknowledgment.—The authors acknowledge the support of the National Science Foundation through Grant No. GY-3779 and the support of Berea College.

(5) H. Haubenstock and C. VanderWert, *J. Org. Chem.*, **29**, 2993 (1964).

(6) C. R. Hauser and W. B. Renfrow, Jr., *J. Amer. Chem. Soc.*, **59**, 121 (1937).

(7) C. Djerassi and C. T. Lenk, *ibid.*, **75**, 3494 (1952).

A Convenient Procedure for the Methylenation of Olefins to Cyclopropanes

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The methylenation of olefins by the method of Simmons and Smith,[2] utilizing methylene diiodide and zinc–copper couple, provides a most convenient and much used entry into the cyclopropane field. However, in spite of various modifications,[3,4] the experimental procedure still requires the preparation of rather irreproducible zinc–copper reagents.

We find that a separate preparation of the zinc–copper couple is not required; a mixture of zinc dust and a cuprous halide is even more effective. This modification reduces the experimental difficulties to the level of those encountered in an ordinary Grignard reaction.

(1) Syntex Postdoctoral Research Fellow, 1968–1969.

(2) (a) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **80**, 5323 (1958); (b) **81**, 4256 (1959).

(3) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

(4) R. S. Shank and H. Schechter, *ibid.*, **24**, 1825 (1959).

The experimental procedure is illustrated by the methylenation of cyclohexene. A mixture of zinc dust (17.0 g, 0.26 mol) and cuprous chloride (2.58 g, 0.26 mol) in 40 ml of ether was stirred and heated to reflux in a nitrogen atmosphere for 30 min. Cyclohexene (10.1 ml, 0.1 mol) was then added, followed by methylene diiodide (10.5 ml, 0.13 mol) and the mixture was maintained at reflux for 24 hr. A 92% yield (gas chromatography) of bicyclo[4,1,0]heptane was obtained. The following olefins were also methylenated: cyclooctene (94%), cyclododecene (79%), and styrene (69%). The cuprous halide could be replaced by copper powder, although yields were slightly lower (87% from cyclohexene). In an alternative procedure the reagent was preformed from the cuprous chloride, zinc dust, and methylene diiodide and refluxed for a further 30 min before addition of the olefin.

Registry No.—Zinc, 7440-66-6; cuprous chloride, 7758-89-6.

Cycloaddition Reactions of Cyclopropanones[1]

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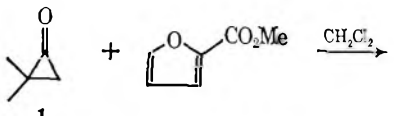
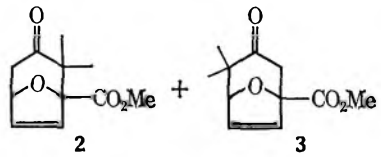
Cyclopropanones have been shown to undergo 2 + 2 → 4, 3 + 2 → 5, and 3 + 4 → 7 cycloaddition reactions.[5-14] In addition, similar 3 + 4 → 7 adducts have been reported in several studies of supposed Favorskii intermediates.[15-17] We wish to report several new examples of these cycloadducts.

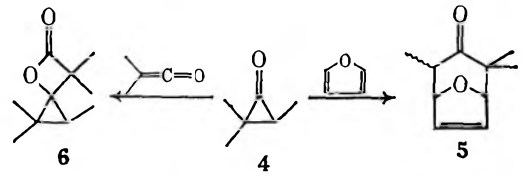
2,2-Dimethylcyclopropanone (**1**) reacts with 2-carbomethoxyfuran to form adducts **2** and **3** in the ratio of *ca.* 7.5:1 in greater than 70% yield (eq 1). 2,2,3-Trimethylcyclopropanone (**4**) reacts with furan to form adduct **5** in over 90% yield and with dimethylketene to form adduct **6** as the only product (eq 2).



1

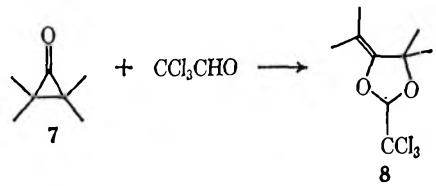


2 **3** (1)



6 **4** **5** (2)

Tetramethylcyclopropanone (**7**) reacts with chloral to form adduct **8** as the only product (eq 3).



7 **8** (3)

These adducts were characterized unambiguously on the basis of spectral data (see Experimental Section). Their spectral characteristics correlate very well with previously reported adducts.[8]

The results reported here, when combined with previous work on the cycloaddition of cyclopropanones,[9-14] clearly demonstrate the generality and synthetic value of these reactions.

Experimental Section

1-Carbomethoxy-2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (2) and 1-Carbomethoxy-4,4-dimethyl-8-oxabicyclo[3.2.1]-oct-6-en-3-one (3).—2-Carbomethoxyfuran (2 ml, 18.7 mmol) was mixed with a CH_2Cl_2 solution (7 ml) of 2,2-dimethylcyclopropanone (13.3 mmol), and the mixture was left at room temperature for several days. Removal of the solvent on a "Roto-Vap" followed by preparative vpc (6 ft × 3/8 in., 20% SE-30, Chromosorb P, 200 ml of He/min, 198°) resulted in the isolation of a mixture of **2** and **3**. Adduct **2** was the major isomer by ≈7.5 to 1. Attempts to separate the two isomers by vpc ($\beta\beta\beta$, Carbowax, diisodecyl phthalate) or by tlc (silica or alumina) were unsuccessful. Adduct **2** had the following nmr spectrum (CCl_4–TMS): δ 1.07 (s, 3 H), 1.17 (s, 3 H), 2.50 (AB, 2 H, J_{AB} = 17 Hz, $\Delta\nu_{AB}$ = 39.4 Hz, low field half split further J = 5 Hz, high field half split further J = 1.5 Hz), 3.77 (s, 3 H), 4.99 (d of t, 1 H, J = 5 and 1.5 Hz), 6.32 (AB, 2 H, J_{AB} = 6 Hz, $\Delta\nu_{AB}$ = 5.9 Hz, high field half split further J = 1.5 Hz). Adduct **3** had the following nmr spectrum (CCl_4–TMS): δ 0.94 (s, 3 H), 1.28 (s, 3 H), 2.60 (AB, 2 H, J_{AB} = 16.5 Hz, $\Delta\nu_{AB}$ = 22.7 Hz), 3.77 (s, 3 H), 4.48 (d, 1 H, J = 1.5 Hz), 6.32. (The olefinic and methoxyl protons of **3** could not be distinguished from those of **2**.) In a previous small-scale reaction, the yield of adducts had been greater than 70% (nmr). Mass spectra of **2** and **3** (75 ev): *m/e* (rel intensity) 210 (M^+, 46), 178 (73), 153 (10), 150 (6), 140 (100), 134 (9), 125 (41), 109 (59), 108 (64), 95 (21), 81 (75), 79 (10), 70 (72), 69 (12), 53 (27), 44 (34), 43 (25), 42 (28), 41 (31), 40 (37), 39 (20).

2,2,4-Trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (5).—A dilute (2–3%) CH_2Cl_2 solution of 4[18] (15 ml) was mixed with 5 ml of purified furan (~69 mmol). After 1 hr at room temperature, evaporation of the solvent followed by preparative vpc (6 ft. × 3/8 in., 22% Carbowax 20M, Chromosorb P, 200°, 120 cc of He/min) led to the isolation of adduct **5** which was identified by the following spectral properties: ir ν_{max}^{neat} 1715 (C=O), 1380

(1) (a) Cyclopropanones. XVIII. Paper XVII: S. S. Edelson and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 2770 (1970). (b) The authors wish to thank the U. S. Air Force Office of Scientific Research for their generous support of this work (Grants AFOSR-66-1000 and AFOSR-68-1381). A gift from the Upjohn Co. is also gratefully acknowledged.

(2) Alfred P. Sloan Fellow, 1966–1970.

(3) National Science Foundation Trainee, 1965–1966; National Science Foundation Predoctoral Fellow, 1966–1969.

(4) National Science Foundation Trainee, 1967–1968; Ferguson Teaching Fellow, 1968–1969.

(5) R. C. Cookson, M. J. Nye, and G. Subrahmanyam, *Proc. Chem. Soc. London*, 144 (1964).

(6) H. G. Richey, J. M. Richey, and D. C. Clagett, *J. Amer. Chem. Soc.*, **86**, 3906 (1964).

(7) N. J. Turro, W. B. Hammond, and P. A. Leermakers, *ibid.*, **87**, 2774 (1965).

(8) See N. J. Turro, S. S. Edelson, J. R. Williams, T. R. Darling, and W. B. Hammond, *ibid.*, **91**, 2283 (1969), and references therein.

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(10) W. B. Hammond and N. J. Turro, *J. Amer. Chem. Soc.*, **88**, 2880 (1966).

(11) N. J. Turro and W. B. Hammond, *Tetrahedron*, 6017 (1968).

(12) N. J. Turro, S. S. Edelson, J. R. Williams, and T. R. Darling, *J. Amer. Chem. Soc.*, **90**, 1926 (1968).

(13) N. J. Turro and J. R. Williams, *Tetrahedron Lett.*, 321 (1969).

(14) N. J. Turro and S. S. Edelson, *J. Amer. Chem. Soc.*, **90**, 4499 (1968).

(15) A. W. Fort, *ibid.*, **84**, 4979 (1962).

(16) R. C. Cookson and M. J. Nye, *Proc. Chem. Soc.*, 129 (1963).

(17) R. C. Cookson, M. J. Nye, and G. Subrahmanyam, *J. Chem. Soc., C*, 473 (1967).

and 1360 cm^{-1} (*gem*-dimethyl), 725 cm^{-1} (>C=C<); nmr (CCl_4–TMS) δ 6.36–6.13 (m, 2 H), 4.65 (d, 1 H, J = 5 Hz), 4.29 (s, 1 H), 2.81 (d of q, 1 H, J = 7, 5 Hz), 0.89 (s, 3 H), 0.88 (d, 3 H, J = 7 Hz), 1.26 (s, 3 H); mass spectrum (75 eV) m/e (rel intensity) 166 (M^+, 37), 151 (15), 123 (6), 110 (12), 96 (81), 95 (67), 81 (100), 70 (31), 68 (13), 67 (22), 55 (23), 53 (17), 42 (28), 41 (65), 39 (64).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found: C, 72.10; H, 8.67.

From nmr, **5** appears to be a single isomer; however, of the four possible isomers, we do not know which isomer we have isolated.

1,1,2,6,6-Pentamethyl-5-oxo-4-oxaspiro[2.3]hexane (6).—To a 10% solution of dimethylketene (*ca.* 30 mmol) in CH_2Cl_2 was added a CH_2Cl_2 solution of **4**[18] (*ca.* 20 mmol). The solution was allowed to stand for 6 days at −78°. The resulting solution was concentrated and analyzed by vpc (6 ft × 1/4 in., 22% Carbowax 20M, Chromosorb P, 200°, 120 cc of He/min). The major product was collected and identified as adduct **6** by the following spectral properties: ir $\nu_{max}^{CCl_4}$ 1830 (C=O), 1385 and 1365 cm^{-1} (*gem*-dimethyl); nmr (CCl_4–TMS) δ 1.39 (s, 3 H), 1.29 (s, 3 H), 1.13 (s, 3 H), 1.09 (s, 3 H), 1.06 (d, 3 H, J = 7 Hz), 0.82 (q, 1 H, J = 7 Hz); mass spectrum (75 eV) m/e (relative intensity) 168 (3, M^+), 153 (2), 124 (1) 123 (2), 108 (7), 70 (100), 55 (25), 42 (41).

5,5-Dimethyl-4-isopropylidene-2-trichloromethyl-1,3-dioxolane (8).—A dilute (<1%) CH_2Cl_2–*n*-pentane solution (10 ml) of tetramethylcyclopropanone was mixed with chloral (1 ml, 10.3 mmol) and left at room temperature overnight. Removal of the solvent on a "Roto-Vap" followed by preparative vpc (6 ft × 3/8 in., 20% SE-30, Chromosorb P, 200 ml of He/min, 210 and 175°) then resulted in the isolation of **8**: ir $\nu_{max}^{CCl_4}$ 1710 cm^{-1}; nmr (CCl_4–TMS) δ 1.46 (s, 3 H), 1.63 (s, 6 H), 1.67 (s, 3 H), 5.39 (s, 1 H); mass spectrum (75 eV) m/e (rel intensity) 258 (M^+, 8), 153 (2), 141 (33), 131 (5), 112 (7), 97 (10), 95 (100), 84 (51), 69 (50), 67 (16), 55 (15), 44 (39), 43 (34), 41 (32), 40 (31), 39 (12).

Registry No.—**2**, 24165-15-9; **3**, 24165-11-5; **5**, 24165-12-6; **6**, 24165-13-7; **8**, 24165-14-8.

(18) N. J. Turro and R. B. Gagosian, *J. Amer. Chem. Soc.*, in press.

Glycidyltrimethylammonium Chloride and Related Compounds

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In 1904, Schmidt and Hartmann reported[1] obtaining glycidyltrimethylammonium chloride (I) as a noncrystallizable syrup of unspecified epoxide content by reacting epichlorohydrin with excess trimethylamine in ethanolic solution. The yield was low and the main product was the bis salt, 2-hydroxypropane-1,3-bis(trimethylammonium chloride). Two decades earlier, Reboul had claimed[2] that the viscous syrup which was isolated when equal volumes of epichlorohydrin and triethylamine were heated to 100° was the homologous glycidyltriethylammonium chloride.

More recently a patent has issued to Paschall of the Corn Products Co. which claims the use of the product[3] from the interaction of epichlorohydrin with trimethylamine for the etherification of starch. According to Paschall, I was obtained[3] as a viscous syrupy distillation residue by treating epichlorohydrin with trimethylamine in aqueous solution at 25°. We have found that the syrup obtained by Paschall's procedure has only 40–60% of the theoretical epoxy oxygen value. On standing for 24 hr at 25°, the epoxide content declined to about half of its original value and, after 1 week at 25°, no significant (<5%) amount of epoxide remained. In a recent publication,[4] Burness has observed that reaction of epichlorohydrin with trimethylamine in acetonitrile at 25° affords N-(3-hydroxy-1-propenyl)trimethylammonium chloride (II, 87% yield) rather than I. We now report the preparation of

$$(CH_3)_3\overset{Cl^-}{N}CH{=}CHCH_2OH$$
II

pure, crystalline, stable glycidyltrimethylammonium chloride (I) for the first time.

Results

Glycidyltrimethylammonium Chloride.—The reaction of epichlorohydrin and trimethylamine to form I is best carried out in an aprotic solvent in which I is essentially insoluble. With excess epichlorohydrin as solvent (4.5:1 mole ratio), the reaction takes place very readily at 25° and I is formed in nearly quantitative yield and conversion. The product, a hygroscopic sharp-melting white crystalline material, is of 98% or better purity on the basis of epoxide content. When the reaction is conducted in other dry aprotic oxygenated solvents such as ethers, ketones, and esters, product of 95–97% epoxide content is isolated in nearly quantitative yield but only 50–75% conversion. The results of several experiments in which 0.25 mol of each reactant was stirred at 25–30° in 100–125 ml of the stipulated solvent for the specified period of time are summarized in Table I. The rate of the reaction is

TABLE I
REACTION OF EPICHLOROHYDRIN WITH TRIMETHYLAMINE
(0.25 mol of each reactant in 100–125 ml of solvent at 25–30°)

Solvent	Reaction time, hr	% conversion of epichlorohydrin	% yield of I	% purity (epoxide)
Acetone	35	74	97	96
Tetrahydrofuran	60	60	95	96
Dimethoxyethane	60	56	97	97
Ether	60	40	97	97
Ethyl Acetate	35	40		95
Hexane	60	15	98	96
Ethanol	16	95		20

considerably greater in acetone (ϵ 21) than in other oxygenated aprotic solvents of lower dielectric constant (ϵ 4–7). In hexane (ϵ 1.9) the reaction proceeds at such a slow rate as to be impractical although product of good quality is obtained. In contrast, when the

$$(CH_3)_3N + CH_2\text{—}CHCH_2Cl \longrightarrow (CH_3)_3\overset{Cl^-}{N}CH_2CH\text{—}CH_2$$
(O) (O)
I

(1) E. A. Schmidt and H. Hartmann, *Ann.*, **337**, 116 (1904).
(2) E. Reboul, *Compt. Rend.*, **93**, 423 (1881).
(3) E. F. Paschall, U. S. Patent 2,876,217 (1959).
(4) D. M. Burness, *J. Org. Chem.*, **29**, 1862 (1964).

reaction is carried out in a protic solvent such as ethanol in which I is soluble, the viscous syrup which is obtained has less than 20% of the theoretical epoxide content. Reaction in *t*-butyl alcohol solvent at 25° affords[4] II (80% yield) rather than I.

In aprotic solvents, epoxide of optimum purity (97–98%) is obtained when the reaction temperature is maintained below 30°. In dimethoxyethane, the epoxide content falls to 85–90% of theory at 50° and to less than 70% at 65°. Small amounts of water in the reaction medium have a deleterious effect upon oxirane ring content of I. Thus, in 99% dimethoxyethane–1% water, product of 78% epoxide content is obtained, whereas material of 97% purity is isolated from the anhydrous medium.

When isolated in a pure crystalline form, I is surprisingly stable under ordinary conditions. After 1 week at 25°, the epoxide value remained 97%. Only after 1 month at 25° did noticeable decomposition occur with the epoxide content falling to 92%. Epoxide loss is entirely arrested by storage at 0° even after a 1-year period of time.

Glycidyltriethylammonium Chloride.—The reaction of epichlorohydrin with triethylamine to form glycidyltriethylammonium chloride (III) is best carried out using equal weights of the reactants and no solvent at 25°. Using this procedure, crystalline III of 98% purity is obtained in good yield. However, this sterically hindered amine reacts so slowly that, even after 90 hr, the conversion is only 20%. When the reaction is carried out either in excess epichlorohydrin or at 50 instead of 25°, material of low (50–70%) epoxide content is obtained. Indeed, at 80° with equal weights of reactants, the product contains no significant epoxide. On this basis, it is believed that the material prepared by Reboul[2] was not III but probably a crude homolog of II.

Glycidyltrimethylammonium Bromide.—Glycidyltrimethylammonium bromide is obtained in 92% yield as a sharp melting crystalline material by reaction of epibromohydrin with trimethylamine in dimethoxyethane solvent at 20°. The compound which has an epoxide value that is 98% of theory appears to be quite stable when stored at 0°.

Discussion

The most important factor in determining the course of the reaction between epichlorohydrin and trimethylamine is the solubility of the initially formed glycidyltrimethylammonium chloride (I) in the reaction medium. In excess epichlorohydrin, the solubility is so low (0.02 g/100 g) as to preclude further reaction of I with itself, solvent, or amine. The excellent results observed in other aprotic oxygenated solvents are also attributed to the low solubility of I in these media.[5] However, in an ethanolic medium the solubility is so great (40 g/100 g) that I is available for further reaction with itself or with solvent or with amine. The result is that a complex mixture of products (I, chlorohydrin[3] of I, etherification product, II, and other unidentified material) is obtained. A similarly complex mixture of products is obtained when the reaction is carried out in aqueous solution. The solubility of I in water is greater than 100 g/100 g of solvent.

In *t*-butyl alcohol, I is also quite soluble (about 15 g/100 g) but in this case the reaction is fairly selective (80% yield) to give II since the alcohol, itself, is relatively unreactive. The intermediacy of I in the formation of II has been confirmed by the ease with which I rearranges to II in *t*-butyl alcohol solvent at 25° in the presence of trimethylamine. Even in the absence of added amine, I is converted into II in *t*-butyl alcohol at 80°. The presence of small amounts of amine formed by decomposition of I is detectable after one

$$(CH_3)_3\overset{Cl^-}{N}CH_2CH\text{—}CH_2 \xrightarrow{(CH_3)_3N} (CH_3)_3\overset{Cl^-}{N}CH{=}CHCH_2OH$$
(O)

hour at 80°. Thus, even trace amounts of the amine can apparently catalyze the rearrangement of I to II at 80°. Burness has also established[4] the intermediacy of the epoxide in the formation of II in his experiments carried out in acetonitrile solution using a sample of I supplied by us. His results confirm the importance of the solubility factor in product determination as the solubility of I in acetonitrile at 25° is greater than 3 g/100 g of solvent.

It should be emphasized that the solubility of I in the reaction medium is not the only factor which appears to be important in the determination of product composition. Thus, the yield of I observed in aqueous solution[3] is five times that observed in acetonitrile[4] despite the fact that the solubility of I in water is 30 times that in the nitrile. Increased basicity of trimethylamine in acetonitrile over that in water may increase the rate of the base-catalyzed isomerization of I to II in nitrile solvent. The water has a "leveling effect" on the basic strength of the amine. Solvation of I by water may also be important in slowing down the rate of conversion of I to II in aqueous solution.

Experimental Section

Glycidyltrimethylammonium Chloride.—The reaction vessel was a 1-l. flask equipped with stirrer, gas addition tube, and a condenser cooled to −20°. Trimethylamine (95 g, 1.61 mol) was added slowly over a 1-hr period to 600 g (7 mol) of epichlorohydrin maintained at −10 to 0° by external cooling. Stirring was continued at 20–25° for 5 hr. The crystals which separated were collected by filtration in a drybox and washed several times with ether. After drying *in vacuo* at 35° for 1 hr, the product weighed 239 g (98%) and melted at 139–141°. The product had an epoxide value[6] of 0.645 equiv/100 g (98% of theory).

Anal. Calcd for $C_6H_{14}ONCl$: C, 47.5; H, 9.2; Cl, 23.4; N, 9.2. Found: C, 47.2; H, 9.4; Cl, 23.6; N, 9.1.

Glycidyltriethylammonium Chloride.—A mixture of 30 g (0.33 mol) of triethylamine and 30 g (0.32 mol) of epichlorohydrin was stirred at 25° for 90 hr. The oil which separated (lower layer) was washed three times with ether in a drybox. The product which crystallized on cooling, mp 32–35°, weighed 9 g (95% yield based on converted epichlorohydrin) after drying *in vacuo* at 35° and had an epoxide value of 0.51 equiv/100 g (98% of theory). Analysis of the upper layer by gas–liquid chromatography showed that 24 g (20% conversion) of epichlorohydrin was recovered.

Anal. Calcd for $C_7H_{16}ONCl$: C, 50.6; H, 9.9. Found: C, 50.4, H, 9.8.

(5) The solubility of I in oxygenated organic media apparently increases with increasing temperature and the presence of increasing amounts of water. Hence, the poor product purity observed at 65° or in the presence of 1% water is easily rationalized.

(6) O. F. Lubatti, *Chem. Ind.* (London), **51**, 1361T (1932).

Glycidyltrimethylammonium Bromide.—A solution of 15 g (0.25 mol) of trimethylamine and 29 g (0.21 mol) of epibromohydrin in 70 ml of dimethoxyethane was stirred at 0–20° for 18 hr. External cooling was necessary to maintain the temperature. The white crystals were collected by filtration and washed with ether in a drybox. After drying *in vacuo* at 35°, the halide weighed 38 g (92% yield), melted at 151–153°, and had an epoxide value of 0.50 equiv/100 g (98% of theory).

Registry No.—I, 3033-77-0; glycidyltriethylammonium chloride, 15876-88-7; glycidyltrimethylammonium bromide, 13895-77-7.

The Nature of the Activated Complex in the Permanganate Oxidation of Phenylmethanenitronate Anions[1,2]

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The neutral or alkaline permanganate oxidation of nitronate anions has been shown to give excellent yields of aldehydes and ketones.[3,4] Kinetic studies in our laboratories of phenylmethanenitronate anion (I),[5] cyclohexanenitronate anion (II), and cyclopentanenitronate anion (III)[6] have shown in strongly alkaline media[7] that the reaction is zero order in hydroxide ion, first order in permanganate ion, and first order in nitronate anion. The $\Delta H^{\pm}$ for the oxidation of I is 7.5 kcal/mol and $\Delta S^{\pm}$ is -20 eu.[5] The entropy of activation for the oxidation of II and III are -20 and -27.8 eu, respectively.[6] It was proposed that the rate-determining step involves an attack of permanganate at the carbon of the carbon–nitrogen double bond of the nitronate anion[11] to give V, which rearranges to the observed products according to eq 4.[5,6]

$$3R_1R_2C{=}NO_2K + 2KMnO_4 + H_2O \longrightarrow 3R_1R_2C{=}O + 2MnO_2 + 3KNO_2 + 2KOH \quad (1)$$

$$R_1R_2CHNO_2 + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{IV}{R_1R_2C{=}N^+(O^-)O^-} + H_2O \quad (2)$$

$$IV + MnO_4^- \xrightarrow[\text{slow}]{k_2} \underset{V}{\text{cyclic Mn(V) species}} \quad (3)$$

$$V \xrightarrow[\text{fast}]{k_3} \underset{VI}{\text{cyclic Mn(VI) species}} \xrightarrow[\text{fast}]{k_4} R_1R_2C{=}O + MnO_3^- + NO_2^- \quad (4)$$

$$MnO_3^- + MnO_4^- + 2OH^- \xrightarrow[\text{fast}]{k_5} 2MnO_4^{2-} + H_2O \quad (5)$$

Support for the postulated slow step, which involves a change in hybridization from sp^2 to sp^3 at the carbon of the C=N, was obtained from the observation that II reacted six times as fast as III.[1,15] However, the kinetic data are not inconsistent with the formation of VI, *via* the typical permanganate *cis*-cycloaddition mechanism, as the rate-determining step (eq 4). In the hope that the effect of substituents might reveal something about the nature of the activated complex in the rate-limiting step of the permanganate oxidation of I, we investigated the rates of oxidation of several nitronate anions derived from the corresponding *para*-substituted phenylnitromethanes.

Phenyl-, *p*-bromophenyl-, and *p*-methylphenylnitromethane were prepared by treating the respective benzyl bromides with freshly prepared silver nitrite.[16] However, the *m*-methyl derivative appeared to decompose during distillation. *p*-Chlorophenyl-, *p*-nitrophenyl-, and *p*-methoxyphenylnitromethane were prepared by treating their respective cyanides with freshly prepared methyl nitrate.[17] An attempt to prepare the *m*-chloro derivative by this method was unsuccessful.

$$\underset{X}{C_6H_4CH_2CN} + CH_3ONO_2 \xrightarrow{NaOEt} \underset{X}{C_6H_4C(CN){=}NO_2Na} \xrightarrow{\text{hydrolysis}} \underset{X}{C_6H_4CH_2NO_2} + CO_2 \quad (6)$$

The rates were followed spectrophotometrically by observing the disappearance of permanganate (522 mμ) in a stopped-flow reactor.[6] Table I summarizes the rate data.

(1) Previous paper in series: F. Freeman, J. B. Brant, N. B. Hester, A. A. Kamego, M. L. Kasner, T. G. McLaughlin, and E. W. Paull, *J. Org. Chem.*, in press.

(2) Abstracted in part from the M.S. thesis of A. Yeramyan, California State College, Long Beach, Calif., 1969.

(3) H. Shecter and F. T. Williams, Jr., *J. Org. Chem.*, **27**, 3699 (1962).

(4) S. S. Nametkin and O. Madaeff-ssitscheff, *Chem. Ber.*, **59**, 370 (1926).

(5) F. Freeman and A. Yeramyan, *Tetrahedron Lett.*, 4783 (1968).

(6) F. Freeman, A. Yeramyan, and F. Young, *J. Org. Chem.*, **34**, 2438 (1969).

(7) Kinetic studies were performed between pH 12.5 and 13.6. At the higher pH values, phenylnitromethane[8,9] and the nitrocycloalkanes[9,10] are essentially completely converted into the nitronate anions.

(8) W. Kemula and W. Turnowska-Rubaszewska, *Rocz. Chem.*, **37**, 1597 (1963).

(9) F. Freeman and A. Yeramyan, unpublished data, 1969.

(10) P. W. K. Flanagan, H. W. Amburn, H. W. Stone, J. G. Trayham, and H. Shechter, *J. Amer. Chem. Soc.*, **91**, 2797 (1969).

(11) Self-consistent molecular orbital calculations[12,13] and spectroscopic studies[14] have suggested that nitronate anions have essentially a carbon–nitrogen double bond and two equivalent nitrogen–oxygen bonds with low double-bond character.

(12) N. Jonathan, *J. Mol. Spectrosc.*, **7**, 105 (1961).

(13) F. T. Williams, Jr., P. W. K. Flanagan, W. J. Taylor, and H. Shechter, *J. Org. Chem.*, **30**, 2674 (1965).

(14) M. J. Brookes and N. Jonathan, *Spectrochim. Acta*, **25A**, 187 (1969).

(15) III presumably reacts at a slower rate as a result of the increase of I strain (bond opposition forces, compression of van der Waals radii, and distortion of bond angles) in going from IV to V: H. C. Brown and M. Bordowski, *J. Amer. Chem. Soc.*, **74**, 1894 (1952).

(16) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *ibid.*, **77**, 6269 (1955).

(17) A. P. Black and F. H. Babers in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1943, pp 412, 512.

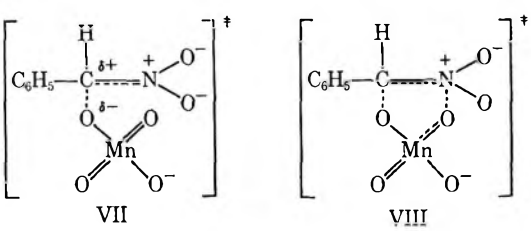
TABLE I

EFFECT OF SUBSTITUENTS ON THE RATE OF OXIDATION AT 1° ($[MnO_4^-] = 4.0 \times 10^{-4} M$, pH = 13.6, $\mu = 0.5$, $\lambda = 522$ mμ)

Substituent	$[R_1R_2C{=}NO_2^-]$ × 10^3 M	k_ψ,[a] sec^{-1}	k_2,[b] M^{-1} sec^{-1}
p-OCH_3	5.01	2.04	405.6
p-CH_3	5.03	1.16	230.6
H	5.00	0.65	130.0
p-Cl	5.00	0.60	120.0
p-Br	5.01	0.44	87.8

[a] Pseudo-first-order rate constant. [b] Second-order rate constant = $k_\psi/[R_1R_2C{=}NO_2^-]$.

Correlation of σ^+ substituent and rate constants (log k_2) gives a ρ^+ of −0.67 with a correlation coefficient (r) of 0.984 and a standard deviation (s) of 0.0546. The magnitude of the reaction constant, although small, is consistent with the formation of a small or negligible positive charge at the benzylic carbon of I. Similar small ρ values have been obtained for the permanganate oxidation of alkenyl anions ($\rho \cong 0$)[18] and for *cis*-1,3-dipolar cycloaddition reactions ($\rho = +0.8$).[19] Consequently, the rate data are consistent with an activated complex which involves partial bonding of permanganate with one or both termini of the carbon–nitrogen double bond[11] with little or no development of positive charge at the benzylic carbon. The partly bridged resonance-stabilized activated complex (VII) or the cyclic manganese (V) ester activated complex (VIII) is entirely consistent with



VII

VIII

the kinetic data.[20] This also implies that the rate-determining step could be eq 3 or 4.[20] However, the entropy of activation (−20 eu), which is smaller than those observed for the permanganate oxidation of alkenyl anions (−27 to −36 eu),[18] is similar to the values for the oxidation of other anions,[1,6] and is more consistent with the formulation of VII as the activated complex. The entropy of activation for *cis*-1,3-dipolar cycloadditions are also generally large and negative (−27 to −49 eu).[19]

(18) K. B. Wiberg and R. D. Geer, *J. Amer. Chem. Soc.*, **88**, 5827 (1966).

(19) R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, London, 1964, p 844.

(20) Although structures VII and VIII are two activated complexes which fit the results, other possible activated complexes can also be drawn.

Experimental Section

All melting points are uncorrected and were determined on a Thomas–Hoover apparatus. Ultraviolet spectra were taken in a Beckman DK-2A spectrophotometer, and the kinetics were performed with a Beckman DU spectrophotometer and a Bristol strip-chart recorder.

TABLE II

PREPARATION AND PHYSICAL PROPERTIES OF PHENYLNITROMETHANE DERIVATIVES

Phenylnitromethane derivative	Method of preparation	Mp or bp (mm), °C	Lit. mp or bp (mm), °C	$n^{20}D$	Lit. $n^{20}D$
p-H	A[a,b]	68–71 (0.5)	77–79 (1)[c]	1.5322	1.5315[c]
p-Br	A[a]	51.0–51.5	50[d]		
p-CH_3	A[a]	99–102 (3)	99 (3)[e]	1.5281	1.5278[e]
m-CH_3[f]	A[a]				
p-Cl	B[g,h]	29.5–30.0	33[i]		
m-Cl[j]	B[g]				
p-OCH_3	B[g]	135–138 (2)	106–108 (6)[a,k]	1.5460	1.5400[a]
p-NO_2[l]	B[g]	88.5–89.0	91–92[e]		

[a] Reference 16. [b] Corresponding benzyl bromide and silver nitrite. [c] Reference 21. [d] Reference 22. [e] Reference 23. [f] Product decomposed during distillation. [g] Reference 17. [h] Corresponding benzyl cyanide and methyl nitrate. [i] Reference 24. [j] No product was obtained in one experiment.[9] [k] Reference 25. [l] Basic solution gave an orange color.

Phenylnitromethane Derivatives.—The phenylnitromethanes used in this work were prepared by the methods indicated in Table II, which also lists physical properties and literature values.[21–25]

Reagents.—Distilled water was purified by passing through two type R-2 ion-exchange columns.[26] Standard volumetric (Acculute) potassium hydroxide (CO_2 free) concentrate was diluted to the specified volume for the desired pH. Potassium permanganate stock solutions were also prepared from standard volumetric solutions (Acculute). The stock solution was stored under nitrogen and the absorbancy index was checked before each set of kinetic runs. Reagent grade sodium chloride (Mallinckrodt) was used without further purification to adjust ionic strength. All solutions were prepared immediately before use, and the pH was measured potentiometrically.

Kinetic Method.—Because of the rapid rate of oxidation, the kinetics were determined by observing the disappearance of permanganate at 522 mμ, in a stopped-flow reactor.[1,6] All studies were performed under pseudo-first-order conditions. The pseudo-first-order rate constants (k_ψ) were obtained from the slopes of plots of $-\ln[\log (T_\infty/T)]$ *vs.* time and were calculated on an IBM 360 computer.[27,28] T_∞ is the per cent transmission, after at least three half-lives, at a point just before colloidal manganese dioxide begins to form. The rate constants are the average of two or more determinations.

Registry No.—IV (R_1 = CN; R_2 = p-$OCH_3C_6H_5$), 12413-22-8; IV (R_1 = CN; R_2 = p-ClC_6H_5), 12413-20-6; IV (R_1 = H; R_2 = p-$CH_3C_6H_5$), 12413-21-7; IV (R_1 = H; R_2 = C_6H_5), 12413-18-2; IV (R_1 = H; R_2 = p-BrC_6H_5), 12413-17-1.

(21) M. Konovalow, *Chem Zentr.*, **70**, 1238 (1899).

(22) J. Wisliceus and B. Elvert, *Chem. Ber.*, **41**, 4129 (1908).

(23) J. S. F. Pode and W. A. Waters, *J. Chem. Soc.*, 717 (1956).

(24) J. von Raalte, *Rec. Trav. Chim. Pays-Bas*, **18**, 392 (1899).

(25) p-Methoxyphenylnitromethane has been reported as an orange or yellow liquid.[16] We observed that it is a colorless liquid which is unstable and becomes yellow during distillation and during storage at −60 to −70°.

(26) Illinois Water Treatment Co., Rockford, Ill.

(27) K. B. Wiberg, "Computer Programming for Chemists," W. A. Benjamin, Inc., New York, N. Y., 1965, p 168 ff.

(28) We wish to thank the Western Data Computing Center, University of California, Los Angeles, Calif., for making computer time available to us.

Novel Reactions of Ketoximes with Nitrosyl Chloride[1]

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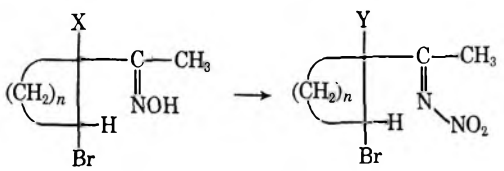
Rheinboldt[2] discovered that nitrosyl chloride[3] would react with aldoximes to give chloronitroso compounds, RCHClNO, or hydroxamic chlorides, ArCCl=NOH, or with ketoximes to give *gem*-chloronitroso compounds. Nitrosyl chloride has been used much more extensively to add to olefins to give β-chloronitroso compounds[3] (normal addition) or in some cases dichloro, chloronitro, or dichloronitroso (anomalous) products.[3a,4] If the β-chloronitroso compound has an α hydrogen, it isomerizes more or less readily to a chloro ketoxime.

We have found a quite different result when compounds of type I are treated with nitrosyl chloride. Two reactions occur. The oximino group is oxidized to



Ia, $n = 3$; X = OCH_3
b, $n = 3$; X = Br
c, $n = 4$; X = OCH_3
d, $n = 4$; X = Br
e, $n = 5$; X = OCH_3
f, $n = 5$; X = Br
g, $n = 4$; X = Br, t-C_4H_9 on C_4

IIa, $n = 3$; Y = OCH_3
b, $n = 3$; Y = Cl
c, $n = 4$; Y = OCH_3
d, $n = 4$; Y = Cl
e, $n = 5$; Y = OCH_3
f, $n = 5$; Y = Cl
g, $n = 4$; Y = Cl

a nitrimine II, a result that has been accomplished by nitrous acid oxidation[5] and by nitrosyl fluoride[6] but not by nitrosyl chloride. In the case of α-bromo ketoximes Ib, d, f, and g, the oxidation is preceded by replacement of bromine with chlorine to give IIb, d, f, and g. The oxidizing action of nitrosyl chloride has been established,[7,8] but the replacement reaction is new.

The mechanism of nitrimine formation (new N–N bond formation at the oximino nitrogen by an electrophilic NO^+ group, followed by an oxygen shift) suggested by Freeman[5,9] and supported by Boswell[6] seems adequate to account for the present results.

Acetylcycloalkenes were synthesized by a Friedel–Crafts reaction[10,11] and converted into unsaturated ketoximes by a standard method. Bromine addition to the oxime gave compounds Ib, d, f, and g. The stereochemistry of the oximes is unspecified in compounds I. Reaction of the dibromo compound with methanol easily replaced the tertiary bromine[12] to give Ia, c, and e. All of the compounds I then gave compounds II with nitrosyl chloride.

The sharp OH absorption at 3600 cm^{-1} characteristic of oximes[13] in *dilute* carbon tetrachloride solution disappears as the reaction occurs. Each of the compounds II show strong bands at 1580 and 1320 cm^{-1} (NO_2) and medium bands at 1640 cm^{-1} (C=N), characteristic of nitrimines.[5,14] The ultraviolet spectrum of each compound gave a low intensity absorption (ϵ_{max} ~600) at 263–270 mμ[5] in 95% ethanol. The methyl protons in IIa, c, and e gave a chemical shift of δ ~2.03 and those in IIb, d, f, and g gave a shift of δ ~2.2.

The identity of the nitrimine structure was further verified by the reduction of IIa to be corresponding nitramine with lithium aluminum hydride.[5] The halogen was untouched by the strong basic reagent. Compounds IIa and c were hydrolyzed in sulfuric acid solution to the corresponding α-bromo ketones.[15]

Sodium iodide in acetone replaces the α-bromine in Ib, d, and f which is followed by loss of halogen to give 1-acetyl-1-cycloalkene oxime. In contrast, compound IId does not react with sodium iodide in acetone nor is chlorine or bromine displaced by alcoholic silver nitrate solution. The bromine in Id reacts rapidly with ethanolic silver nitrate. Compound IId is also recovered unchanged after 12-hr reflux with 30% sulfuric acid in contrast to the easy hydrolysis of other nitrimines.[16] The remarkable stability of chlorobromo compound IId and the lability of the α-bromine in Id certainly suggests that bromine displacement in Id occurs before oxidation to nitrimine.

Experimental Section

1-Acetylcyclopentene.—1-Acetylcyclopentene was prepared by the method of Casals[17] in 77% yield. The compound was identified by its 2,4-dinitrophenylhydrazone derivative, mp 201–203°[17] and ir spectrum. The oxime was prepared (yield 41%) by a well-known procedure[18] and sublimed at low pressure for the analytical sample.

Other acetylcycloalkenes were prepared by a Friedel–Crafts procedure[11] and their oximes by a standard method.[18]

The acetylcycloalkenes showed the following absorption in the ir spectra (cm^{-1}, dilute CCl_4): vinyl CH, 3050–3075 (s); C=O, 1720 (s), 1670–1675 (s); C=C, 1640–1650 (w). The nmr spectrum of 1-acetyl-1-cyclopentene follows (CCl_4): δ 6.68 (s, 1), 2.25 (s, 3), 1.8–2.7 (m, 6). The nmr spectra of other acetylcycloalkenes were consistent with these chemical shifts for vinyl CH, acetyl CH_3 groups, and methylene groups.

(1) Supported in part by Public Health Service Grant CA-07521 from the National Institutes of Health. The Varian A-60A nmr spectrometer used in this research was purchased through a National Science Foundation Instrument Grant.

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(3) (a) P. P. Kadzyauskas and N. S. Zefirov, *Russ. Chem. Rev.*, **37**, 543 (1968); (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, pp 748–755; (c) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951).

(4) K. A. Oglobin, V. N. Kalikhevich, A. A. Potekhin, and V. P. Semenov, *Zh. Obshch. Khim.*, **34**, 170 (1964).

(5) J. P. Freeman, *J. Org. Chem.*, **26**, 4190 (1961); **27**, 1309 (1962); *Chem. Ind* (London), 1624 (1960).

(6) G. A. Boswell, Jr., *J. Org. Chem.*, **33**, 3699 (1968).

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(8) D. T. Manning and H. A. Stansbury, Jr., *J. Amer. Chem. Soc.*, **81**, 4885 (1959).

(9) See also T. Wieland and D. Grimm, *Ber.*, **96**, 275 (1963).

(10) R. E. Christ and R. C. Fuson, *J. Amer. Chem. Soc.*, **59**, 893 (1937).

(11) N. Jones, H. T. Taylor, and E. Rudd, *J. Chem. Soc.*, 1342 (1961).

(12) O. Wallach and E. Evans, *Ann.*, **360**, 44 (1908).

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(15) E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 2301 (1953).

(16) J. W. Suggitt, G. S. Myers, and G. F. Wright, *J. Org. Chem.*, **12**, 373 (1947).

(17) P.-F. Casals, *Bull. Soc. Chim. Fr.*, 253 (1963).

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TABLE I

PROPERTIES OF METHYL CYCLOALKYL KETOXIMES

1-Acetyl derivative	Yield, %	Oxime Mp, °C	Oxime Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Cyclopentene	77	94–95.5	41	67.17	8.86	11.19	67.32	8.74	10.94
Cyclohexene	73	63.0–63.5	73	69.03	9.41	10.07	69.30	9.57	10.21
Cycloheptene	56	59–60	62	70.49	9.87	9.13	70.70	9.69	9.10
4-*t*-Butylcyclohexene		156–157	38	73.78	10.85	7.17	73.80	10.79	7.13

TABLE II

PROPERTIES OF COMPOUNDS I AND II

Compd	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Br	Found, % C	Found, % H	Found, % N	Found, % Br
Ia	37	106–107	40.69	5.98	5.93		40.65	6.27	5.93	
Ib	77	77–78	29.49	3.89	4.92		29.33	4.08	4.96	
IIa		69–70	36.23	4.95	10.57		36.50	5.20	10.40	
IIb		57–58	31.20	3.76	10.42		31.43	3.76	10.54	
Ic	90	133–134.5	43.23	6.41	5.60	31.96	43.45	6.46	5.53	32.09
Id	100	118–119	32.15	4.38	4.68	53.46	32.41	4.49	4.78	53.57
IIc	89	71–73	38.73	5.41	10.03		38.78	5.62	10.07	
IId	40	57–58	33.87	4.61	9.87		33.65	4.26	9.62	
Ie	30	130.5–132	45.45	6.87	5.32		45.47	6.77	5.24	
If	44	100–101	34.52	4.83	4.47		34.94	4.79	4.59	
IIe		Oil								
IIf	15	60.5–62	36.31	4.74	9.41		36.47	4.74	9.31	
Ig	20	134–135.5	40.56	5.96	3.94		40.54	5.68	3.67	
IIg	40	92–93	42.41	5.94	8.24		42.53	5.79	8.22	

The corresponding oximes gave the following absorptions in the ir spectra (cm^{-1}, dilute CCl_4): oxime OH, 3590 or 3610 (s); H bond, 3200–3300; C=N, C=C, 1630–1650. Nmr spectrum of 1-acetyl-1-cyclopentene oxime (CCl_4): δ 9.8 (s, 1, NOH), 6.01 (m, 1), 2.0 (s, 3), 1.8–2.8 (m, 6). Other oximes had consistent nmr patterns. See Table I for analyses.

Methyl 1,2-Dibromo-1-cyclopentyl Ketoxime (Ib).—Addition of bromine in carbon tetrachloride to the corresponding ketoxime gave the dibromo derivative in 77% yield. The solvent was removed and the oxime was recrystallized from a carbon tetrachloride–pentane mixture, mp 77–78.5°. The compound decomposed when exposed to light and was kept in a sealed container.

Other dibromo compounds were obtained in quantitative yields by the same method. When the corresponding dibromo ketones were oximated, low yields or no yields of dibromo ketoximes were obtained and the compound lost hydrogen bromide continuously.[19] The dibromo oximes gave the following ir absorption bands (cm^{-1}, dilute CCl_4): oxime OH, 3580–3600 (s); C=N, 1650–1670 (w). The nmr spectrum of Ib follows (CCl_4): δ 4.7 (d, 1, CHBr), 2.1 (s, 3), 1.9–3.0 (m, 6). The nmr spectra of the other dibromo compounds, Id, f, and g are consistent with the spectra of Ib.

Sodium iodide (75 mg, 0.5 mmol) was dissolved in 10 ml of acetone and shaken with 36 mg (0.12 mmol) of Id. Sodium bromide precipitated at once, but the mixture was allowed to stand overnight. The white precipitate was filtered and acetone was removed on a rotatory evaporator. The remaining oil was taken up in water and extracted with carbon tetrachloride. Evaporation of the carbon tetrachloride gave 12 mg (70%) of a solid, identified as 1-acetylcyclohexene oxime by comparison with the nmr spectrum of an authentic sample (CCl_4): δ 1.97 (s, 3), 6.12 (m, 1).

In contrast, IId was recovered unchanged after refluxing with sodium iodide in acetone for 2.5 hr and standing overnight.

Methyl 1-Methoxy-2-bromo-1-cyclopentyl Ketoxime (Ia).—Compound Ib (2 g, 7.0 mmol) (above) was dissolved in 30 ml of absolute methanol and stirred for 20 hr at ambient temperatures. The solution was poured into ice and the precipitate was collected and dried, yield 0.61 g (37%), mp 104–106°. The analytical sample was recrystallized twice from aqueous methanol, mp 106–107°.

The yield was not improved by adding anhydrous sodium carbonate to the reaction mixture. Other bromomethoxy ketoximes were prepared in similar fashion. Addition of N-bromosuccimmide in methanol to 1-acetyl-1-cyclohexene gave the corresponding bromomethoxy ketone, but we were unable to convert this compound into the oxime, Ic.

Ir spectra of the bromomethoxy ketoximes were taken in dilute carbon tetrachloride solution: NOH, 3590–3600 (s); C=N, 1650 (w); C—O, 1060–1090. Nmr spectrum of Ia follows (CCl_4): δ 4.15 (d, 1, CHBr), 3.1 (s, 3, OCH_3), 1.9 (s, 3, CH_3). In compound Ic, the oximino proton was shifted to δ 10.00 (s) while it was smeared out and not identified in the other bromomethoxy compounds. The CHBr proton appeared at a consistent point.

Methyl 1-Methoxy-2-bromocyclohexyl Nitroketimine (IIc).—Compound Ic (2 g, 8 mmol) was dissolved in 30 ml of carbon tetrachloride at room temperature and a slow stream of nitrosyl chloride gas was bubbled through it. After the solution became dark brown the gas stream was stopped and the solution was allowed to stand for 10 min. Then 2 g of anhydrous sodium carbonate was added and the mixture was allowed to stand for 1 hr. Solids were removed from the green oil by filtration and the solvent was removed on a rotating evaporator. The green oil solidified in the refrigerator, yield 2.0 g (89%), mp 65–66°. Three recrystallizations from pentane and two sublimations gave the analytical sample, mp 71–73°.

Other nitrimines (II) were prepared by a similar procedure. Ir spectra of the nitrimines II were taken in dilute carbon tetrachloride solution: C=N, 1630–1640; NO_2, 1580 and 1320. Nmr spectrum of IIc follows (CCl_4): δ 4.22 (br, 1, CHBr), 3.23 (s, 3, OCH_3), 2.03 (s, 3, CH_3). Other compounds II had spectra consistent with these chemical shifts.

Compound IIc (50 mg) was dissolved in 20 ml of carbon tetrachloride and 1 ml of sulfuric acid was added. The mixture was stirred at room temperature for 1.5 hr. The reaction mixture was neutralized with cold aqueous potassium hydroxide solution and the aqueous layer was extracted with carbon tetrachloride. The solvent was dried with anhydrous magnesium sulfate and then the carbon tetrachloride was removed. One drop of oil remained which had the following properties: ir (cm^{-1}, CCl_4) C=O, 1720 (s); nmr (CCl_4) δ 4.3 (br, 1), 1.5~2.5 (m, 8). The spectrum was identical with that of an authentic sample of α-bromocyclohexanone.[15]

Other properties of compounds I and II appear in Table II.

Reduction of the Nitrimine IIa to a Nitramine.—A solution of 1.38 g (5.2 mmol) of compound IIa in 50 ml of dry ether was added to a slurry of 0.5 g of lithium aluminum hydride[6] in 100 ml of dry ether. The reaction mixture was stirred overnight at ambient temperatures and then refluxed for 24 hr. The mixture was poured into 500 ml of ice water and neutralized with dilute

(19) N. H. Cromwell and P. H. Hess, *J. Amer. Chem. Soc.*, **82**, 136 (1960).

HCl. A yellow solid was extracted with ether and dried, yield 1.05 g (76%). Recrystallization from pentane and sublimation at low pressure gave the analytical sample of 1-α-nitraminoethyl-1-methoxy-2-bromocyclopentane, mp 105–106°, 112° dec.

Anal. Calcd for $C_8H_{15}N_2O_3Br$: C, 35.95; H, 5.66; N, 10.49. Found: C, 36.31; H, 5.72; N, 10.60.

The ir spectrum of the nitramine was taken in dilute carbon tetrachloride (cm^{-1}): NH, 3360; NO_2, 1580 and 1340. The nmr spectrum (CCl_4) follows: δ 4.83 (q, 1, J = 7 Hz), 4.17 (br, 1), 3.4 (s, 3), 1.33 (d, 3, J = 7 Hz). The uv spectrum was taken in 95% ethanol: λ_{max} 232 mμ (ε 8500).[5,20]

Registry No.—Ia, 23042-83-3; Ib, 23042-84-4; Ic, 23042-85-5; Id, 23042-86-6; Ie, 23042-87-7; If, 23042-88-8; Ig, 23042-89-9; IIa, 23042-90-2; IIb, 23042-91-3; IIc, 23042-92-4; IId, 23042-93-5; IIe, 23042-94-6; IIf, 23042-95-7; IIg, 23042-96-8; 1-acetylcyclopentene oxime, 23042-97-9; 1-acetylcyclohexene oxime, 23042-98-0; 1-acetylcycloheptene oxime, 23042-99-1; 1-acetyl-4-*t*-butylcyclohexene oxime, 23043-00-7; 1-α-nitraminoethyl-1-methoxy-2-bromocyclopentane, 23043-01-8.

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Fused-Ring Isoxazolines and Their Isomers[1]

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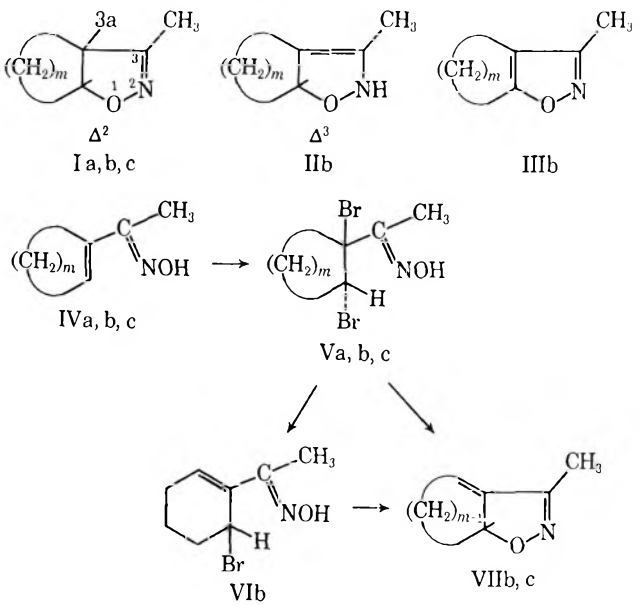
Δ²-Isoxazolines[2] are commonly synthesized from α,β-unsaturated carbonyl compounds by treatment with hydroxylamine. The extensive work of Barnes,[2] Blatt,[2] and von Auwers[2] has shown that the isoxazolines do not arise by direct cyclization (Michael self-addition) of the unsaturated oxime. No Δ³-isoxazoline with an unsubstituted NH[3] has been reported, but a Δ⁴-isoxazoline has recently been postulated as an intermediate in the pathway to an aziridine.[4,5]

We have synthesized a series of Δ²-isoxazolines I, the unsaturated isomeric oximes IV, and the unsaturated isomeric fused ring compounds III and VII. The cycloalkene added the elements of acetonitrile oxide[6,7] to give the Δ²-isoxazolines I. These isoxazolines do not add bromine at room temperature in a period of 24 hr. By oxidation with N-bromosuccinimide[8] Ib was converted in 67% yield to IIIb. The isoxazoline Ib was not oxidized to IIIb by chromic acid in acetic acid,[9] the usual reagent for converting the isoxazoline to an isoxazole. Compounds Ia and Ic gave 3a-bromo derivatives by action of N-bromosuccinimide, but IIIa was not formed by dehydrobromination, and IIIc was too unstable to isolate for analysis. Compound IIIc was identified by ir and nmr spectra (Table I).



Condensation of the 1-acetylcycloalkenes with hydroxylamine in the presence of pyridine gave the unsaturated oximes IV, isomers of I. Compounds IV added bromine (accepted as a *trans* addition) to give *trans*-dibromo derivatives V. The small dipole moment of Vb (0.59 D in benzene) is compatible with the *trans* structure. Acetone oxime, for example, has a dipole moment of 0.88 D.[10] *trans* elimination of HBr to give VIIb is also consistent with the proposed stereochemistry of Vb. Dehydrobromination of Vb with 1 mol of triethylamine in homogeneous medium yielded VIb, identified by nmr spectra and isolated as a glass. Compounds VIIb,c were obtained in a two-phase reaction by shaking solutions of Vb,c in carbon tetrachloride over sodium hydroxide pellets. Compound VIb was also converted to VIIb by the same method. However, compound Va did not undergo the dehydrobromination reactions carried out in a similar way. The allylic bromide VIb is a logical reactive precursor of VIIb. The nonreactivity of Va by comparison with Vb toward dehydrobromination is explained by Brown's I-strain theory.[11] A five-membered ring reluctantly forms an *endo* double bond which would be the case if VIa were a precursor to VIIa. On the other hand, a six-membered ring readily forms an *endo* double bond[11] (VIb) in the pathway to VIIb. Presumably the seven-membered-ring VIc would be subject to internal strain more closely resembling that of the six-membered ring than the five-membered ring. Compound VIc was not isolated but VIIc was isolated and identified.

(1) Support by Public Health Service Grant CA-07521 is gratefully acknowledged. The Varian A-60A nmr spectrometer and the mass spectrometer used in this research were purchased under a National Science Foundation Research Instrument Grant.

(2) Reviewed by A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1962, Chapter 2.

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(4) V. A. Tartakovskii, O. A. Luk'yanov, and S. S. Novikov, *Dokl. Akad. Nauk SSSR*, **178**, 123 (1968).

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(9) G. S. D'Alcontres and G. Lo Vecchio, *Gazz. Chim. Ital.*, **90**, 347 (1960).

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TABLE I

PROPERTIES OF COMPOUNDS Ia–c, IIIb,c, IVa–c, Va–c, VIb, AND VIIb,c[a]

Compound	Mp or bp (mm), °C	Yield, %	Ir, cm^{-1}	Nmr, δ
Ia	53.5–55 (0.3)	37	1620, 1010, 950	1.8 (s, 3), 3.4 (br, 1), 4.9 (br, 1)
Ib	44.5–45.5 (0.14)	58	1620, 1015	1.92 (s, 3), 2.82 (q, 1), 4.25 (q, 1)
Ic	88–90 (3)	46	1625, 1160, 1035	1.8 (s, 3), 3.2 (q, 1), 4.57 (q, 1)
IIIb	37–38 (*1*)	67	1650, 1620	2.21 (s, 3), 2.48 (br, 2), 2.64 (br, 2)
IIIc			1640, 1620	2.08 (s, 3), 2.5–2.9 (br, 2), 2.2–2.5 (br, 2)
IVa	94–95.5	41	3610, 3200, 1630	9.8 (br, 1), 2.0 (s, 1), 6.0 (br, 1)
IVb	63–63.5	73	3610, 3300, 3050, 1640	9.94 (s, 1), 1.95 (s, 3), 6.11 (br, 1)
IVc	59–60	62	3590, 3270, 3040, 1640	1.97 (s, 3), 6.23 (br, 1)
Va	77–78.5	77	3600, 3200, 1650	2.1 (s, 3), 4.7 (br, 1)
Vb	118–119	100	3600, 3350	9.07 (s, 1), 2.07 (s, 3), 4.72 (br, 1)
Vc	100–101	44	3580, 3300, 1670	2.1 (s, 3), 4.81 (br, 1)
VIb		[b]		9.64 (s, 1), 2.00 (s, 3), 4.24 (br), 5.66 (br)
VIIb	54–55 (0.12)	65	1675, 1650, 1580	1.93 (s, 3), 4.46 (br, 1), 5.67 (br, 1)
VIIc	107–108		1670, 1530, 1080	2.13 (s, 3), 4.33 (br, 1), 6.1 (br, 1)

[a] Melting points are corrected. Analyses were satisfactory for all compounds reported except IIIb. Calcd: C, 70.04; H, 8.08; N, 10.21: Found: C, 69.33; H, 8.12; N, 9.83. [b] Obtained as a glass in 96% yield, assuming that the glass is pure.

Reversal of the order of adding reagents to 1-acetylcyclohexene to give the dibromo ketone and then Vb was not successful. Bromine was rapidly decolorized by addition to the unsaturated ketone, but, in the presence of pyridine, hydroxylamine rapidly gave tars with the dibromo ketone. Hydroxylamine hydrochloride alone gave no oxime nor were we successful with Subba Rao's[12] modification. Cromwell and Hess[13] found that a similar α-bromo ketone, 4-biphenyl 1-bromocyclohexyl ketone, gave nearly quantitative elimination of HBr with tertiary amines and even 68% elimination with alcoholic silver nitrate.

We synthesized compounds of type I and the isomeric compounds IV with the thought that one of the series IV might be in equilibrium with the tautomeric Δ^3-fused ring of type II. Catalytic hydrogenation of IVb suggests that the tautomer IIb may be present. In the presence of 10% palladium on carbon, compound IVb (IIb) is rapidly reduced to α-aminoethylcyclohexane. One mole of hydrogen is taken up at a faster rate than the next two, a behavior more consistent with structure IIb than IVb. The first mole of hydrogen added to IVb would be expected to give methyl cyclohexyl ketoxime. A sample of this ketoxime prepared independently from methyl cyclohexyl ketone did not add 2 mol of hydrogen under the same conditions in which IIb (IVb) added 3 mol of hydrogen. The alternate explanation that IVb adds the first mole of hydrogen in the 1,4 manner to give an ene–hydroxylamine (unknown) is not consistent with the instability such a structure would have. The ene–hydroxylamine should rearrange rapidly to methyl cyclohexyl ketoxime, which does not add hydrogen (*vide supra*) or add hydrogen rapidly to give α-aminoethylcyclohexane, but the second and third moles are added more slowly, not more rapidly than the first.

Other reactions described here and ir and nmr spectra, however, are compatible with the single structure IVb.

The experimental procedures are given below for the preparation of the series starting with Ib and IVb. Other members of each series were synthesized in a comparable manner. The properties of the resulting products are given in Table I.

Experimental Section

3-Methyl-Δ^2-hexahydro-1,2-benzisoxazole (Ib).—To a 500-ml round-bottomed flask, 100 ml of cyclohexene, 46.0 g (0.42 mol) of phenyl isocyanate, and 31.5 g (0.42 mol) of nitroethane were added. The solution was stirred while 10 drops of triethylamine in 10 ml of cyclohexene was added very slowly over a period of 0.5 hr. The reaction mixture was stirred at ambient temperatures for 0.5 hr more and was then refluxed for 2 hr. The reaction mixture was cooled and *sym*-diphenylurea was removed. The precipitate was washed with 100 ml of benzene in three portions, and the washings were added to the filtrate. The combined solution was washed twice with 100 ml of water, dried over anhydrous sodium sulfate, and put on a column containing 1 lb of alumina. The first 600 ml of carbon tetrachloride eluted 1.0 g of liquid which was about 60% Ib, 35% dimeric addition product, and a trace amount of dimethylfuroxan. Then 600 ml more of carbon tetrachloride eluted 18.0 g of liquid which was mostly Ib, crude yield 58%. This liquid was dissolved in 150 ml of pentane and washed with 50-ml portions of water until the organic phase became clear. This process removes dimethylfuroxan. The pentane solution was dried over anhydrous sodium sulfate, and pentane was removed on a rotating evaporator. The remaining oil was distilled at reduced pressure: bp 44.5–45.5° (0.14 mm); n^{25}D 1.4810; d^{25}_4 1.033.

In the original work Mukaiyama and Hoshino[14] (and later Backman and Strom[7]) used only 0.5 mol of nitroethane with phenyl isocyanate in generating acetonitrile oxide *in situ*. We obtained better yields with an excess of phenyl isocyanate.

3-Methyl-$\Delta^{2,3a(7a)}$-tetrahydro-1,2-benzisoxazole (IIIb).—To 150 ml of carbon tetrachloride, 3.0 g (0.0216 mol) of Ib and 4.2 g (0.0236 mol) of N-bromosuccinimide were added and gently refluxed for 3 hr. Hydrogen bromide was liberated slowly. The solution was cooled, and precipitated succinimide was removed by filtration. The carbon tetrachloride solution was washed twice with 75 ml of 5% sodium hydroxide solution and then with water until the organic phase became clear. The carbon tetrachloride solution was dried over anhydrous sodium sulfate, and the solvent was removed on a rotating evaporator. The yield was 2.0 g, 67%. The analytical sample was distilled at reduced pressure: bp 37–38° (1 mm), n^{25}D 1.4899. Compound IIIb was unstable upon standing and was analyzed on the day of preparation.

Reduction of Methyl 1-Cyclohexenyl Ketoxime (IVb).—

(12) K. S. R. Krishna Mohan Rao and V. B. Subba Rao, *Indian J. Chem.*, **6**, 66 (1968).

(13) N. H. Cromwell and P. H. Hess, *J. Amer. Chem. Soc.*, **82**, 136 (1960).

(14) T. Mukaiyama and T. Hoshino, *ibid.*, **82**, 5339 (1960).

Methyl 1-cyclohexenyl ketoxime IVb was prepared from 1-acetylcyclohexene[15] by a well-known procedure[16] with a yield of 73%.[17]

Compound IVb (128 mg, 0.92 m mol) was dissolved in 25 ml of 95% ethanol, and 20 mg of 10% palladium on carbon was added. The mixture was placed under 1 atm of hydrogen and stirred magnetically as hydrogen was absorbed. After an induction period of 12 min, 1 mol of hydrogen was taken up in 24 min and 2 mol at a distinctly slower rate in 2.5 hr. The hydrogen uptake stopped and the catalyst was removed. Removal of the solvent on a rotary evaporator left 80 mg of an oil which absorbed CO_2 from the air overnight to give a fine powder. Treatment with aqueous sodium hydroxide gave back the oil, and treatment with hydrochloric acid on another portion gave the hydrochloride of α-aminoethylcyclohexane. Recrystallization from ethanol–ethyl acetate gave the pure hydrochloride, mp 241.5° dec (lit.[18] mp 239–240°). An authentic sample of α-aminoethylcyclohexane hydrochloride (below) did not depress the melting point of this compound and gave identical infrared spectra.

An attempted hydrogenation of 130 mg of methyl cyclohexyl ketoxime, mp 60–61.5°,[19] with 19 mg of 10% palladium on carbon under the same conditions as described for compound IVb (above) resulted in an uptake of less than 0.5 mol in 16 hr. The partially reduced product was not further identified.

The authentic sample of α-aminoethylcyclohexane was prepared from 300 mg of methyl cyclohexyl ketoxime. The ketoxime was dissolved in 30 ml of absolute ethanol, and 5 g of sodium was added in pieces at a rate to keep the alcohol refluxing. Water was finally added and the amine was steam distilled. The hydrochloride (150 mg, 43%) was isolated and recrystallized from ethanol–ethyl acetate, mp 242–243° dec.

Methyl 2-(3-Bromo-1-cyclohexenyl) Ketoxime (VIb).—To a solution of 3.0 g (0.01 mol) of Vb[17] in 100 ml of carbon tetrachloride was added 1.02 g (0.01 mol) of triethylamine dropwise. Immediately, triethylamine hydrobromide was precipitated. The carbon tetrachloride solution was filtered. After reducing the volume of the filtrate to 25 ml using a rotating evaporator without heating, part of the solution was removed for an nmr spectrum of VIb. The low-field hydrogen on oxygen remained, and there was evidence of a trace amount of triethylamine from the easily identifiable ethyl hydrogens. The vinylic proton appeared at δ 5.66 and the allylic proton at δ 4.24. When the solvent was removed completely, an almost colorless glass of 2.10 g remained. The glassy solid was not as soluble in carbon tetrachloride as the starting compound. The nmr spectrum, as just described, was quite different from that of Vb or VIIb (Table I). However, profound decomposition occurred when an attempt was made to distil the glassy solid.

3-Methyl-$\Delta^{2,3a(4)}$-tetrahydro-1,2-benzisoxazole (VIIb).—In 100 ml of carbon tetrachloride 8.0 g (0.0268 mol) of Vb was dissolved, and to the solution was added 4.5 g of sodium hydroxide pellets. The heterogeneous reaction mixture was stirred for 1 hr, and then the precipitate and excess sodium hydroxide were removed by filtration. The filtrate was washed twice with 50 ml of water and dried over anhydrous sodium sulfate. The dried carbon tetrachloride yielded 2.85 g, 65%, of 3-methyl-$\Delta^{2,3a(4)}$-tetrahydro-1,2-benzisoxazole. The analytical sample was distilled at reduced pressure: bp 54–55° (0.12 mm), $n^{25}D$ 1.5174, d^{25}_4 1.0453.

When 2.0 g of VIb was suspended in carbon tetrachloride and treated with 4.5 g of sodium hydroxide pellets, as just described, 1.0 g of VIIb (identical ir and nmr spectra) was obtained.

Registry No.—Ia, 20936-78-1; Ib, 24010-91-1; Ic, 24010-92-2; IIIb, 24010-93-3; IIIc, 24010-94-4; IVa, 23042-97-9; IVb, 23042-98-0; IVc, 23042-99-1; Va, 24010-49-9; Vb, 24010-50-2; Vc, 24010-51-3; VIb, 24010-98-8; VIIb, 24010-99-9; VIIc, 24011-00-5.

(15) R. E. Christ and R. C. Fuson, *J. Amer. Chem. Soc.*, **59**, 893 (1937).

(16) 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.

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(19) M. Godchot, *C. R. Acad. Sci., Paris*, **151**, 1131 (1910), reported mp 60°.

Elimination of Methyl Mercaptan from N-Substituted N′-Cyano-S-methylisothioureas. Evidence for N-Cyanocarbodiimides[1a,b]

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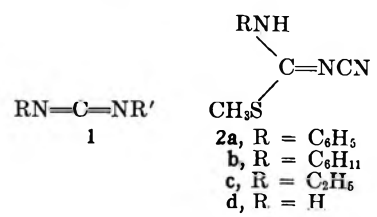
Although carbodiimides with a wide variety of substituents (R and R′ in **1**) have been prepared and characterized,[2] to our knowledge there is little, if any, recorded information on N-cyanocarbodiimides (R or R′ being CN in **1**). We report here evidence for the existence of N-cyanocarbodiimides in solutions resulting from the thermal or metal ion assisted elimination of methyl mercaptan from a series of N-substituted N′-cyano-S-methylisothioureas (**2a–2d**).

During the preparation of several compounds of the general formula **2** for another study,[3] it was found that they readily lose methyl mercaptan at their temperature of melting to yield viscous red oils or red glasses. The elimination of mercaptans from isothioureas was reported as early as 1881 by Will[4] and has been used by Ferris and Schutz[5] for the *in situ* generation of carbodiimides in solution. Ferris and Schutz facilitated the elimination by using a heavy metal ion to effect precipitation of an insoluble metal mercaptide and a base to serve as an acid acceptor. Their technique has been adopted in the present study.



Compounds **2a–2d** were conveniently prepared by the reaction of ammonia or the appropriate amine with dimethylcyanodithioimidocarbonate (**3**) which, in turn, was prepared by the method of Hantzsch and Wolvekamp.[6] The formulation of the isothioureas as shown in **2a–2d** is supported by their elemental analyses and spectral properties, some of which are summarized in Table I. Worthy of comment is the

TABLE I

INFRARED SPECTRA OF ISOTHIOUREAS 2a–2d

Compd	$\bar{\nu}$, cm^{-1} (KBr) NH	C=N	C≡N
2a	3210	1520	2160, 2180
2b	3290	1550	2180
2c	3290	1550	2180
2d	3120, 3310	1530	2180, 2200

(1) (a) Support in part by NASA Grant NsG(T)-21 is gratefully acknowledged. (b) Abstracted from the M.S. Thesis of J. E. Parkinson and the Ph.D. Thesis of D. M. Wieland, West Virginia University, 1969. (c) NASA Trainee, 1965–1968.

(2) F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).

(3) C. G. McCarty and D. M. Wieland, *Tetrahedron Lett.*, 1787 (1969).

(4) W. Will, *Chem. Ber.*, **14**, 1485 (1881).

(5) A. F. Ferris and B. A. Schutz, *J. Org. Chem.*, **28**, 71 (1963).

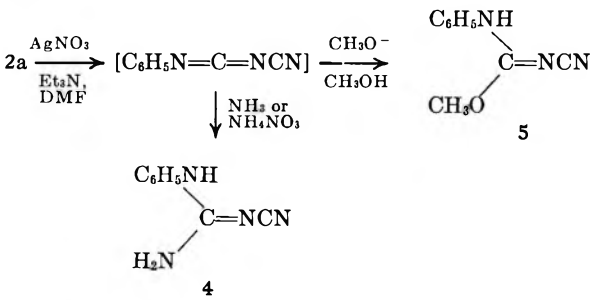
(6) A. Hantzsch and M. Wolvekamp, *Justus Liebigs Ann. Chem.*, **331**, 265 (1904).

nitrile absorption in the ir spectra of **2a** and **2d**. The observation of a shoulder on the main peak in **2a** and a sharp doublet of equal intensity in **2d** is consistent with the conclusion that *syn–anti* isomerism about the C=N bond is possible in these compounds.[3] For **2b** and **2c** either only one isomer is preferred in the crystalline state or the difference in absorption frequencies must be small or nonexistent.

$$\underset{\mathbf{3}}{(CH_3S)_2C{=}NCN} + RNH_2 \xrightarrow{C_2H_5OH} \mathbf{2a\text{–}2d}$$

Each of the compounds **2a–2d**, when taken to its melting point in a vial or capillary tube, gives off methyl mercaptan. As the mercaptan is being evolved, a red, viscous oil forms which becomes quite hard upon cooling. In the case of **2a** analysis of the resulting red glass showed sulfur to be absent.

A variety of procedures was employed to prepare and trap the N-cyanocarbodiimides from **2a–2d**. The salts found to be most useful for these studies were silver nitrate and mercuric chloride. Both are soluble in a fair number of organic solvents and give mercaptide salts insoluble in the same solvents. Triethylamine was used as a proton acceptor in all cases. In a typical experiment, the elimination reaction was carried out by adding a solution of the metal salt to a stirred solution of **2** and triethylamine in the same solvent at room temperature. The metal mercaptide usually started precipitating instantly in finely divided form and was essentially completely formed in 0.5 hr, although stirring was continued, at room temperature, for 1 hr before the red solution was cooled and the solid was collected and weighed. After removal of the precipitate, the desired "trapping" reagent was added to the filtrate to convert the intermediate into a guanidine or isourea derivative. The reactions carried out with **2a**, for example, are shown in the following scheme.



Some of the results of these elimination and trapping reactions for **2a** and the other isothioureas are summarized in Table II. The derivatives isolated were identified by comparisons with authentic samples and by their microanalyses and spectral properties. As can be seen from Table II, the mercaptide formation was usually close to quantitative, suggesting high yields of the reactive intermediate. The lower yields of final products were not unexpected in view of reported yields for similar derivatives from carbodiimides,[5] suspected reactions of the intermediate with itself, and the problems sometimes encountered in the isolation of the products.

Since the same final products could have been obtained by direct reaction of the trapping reagents with the starting isothioureas, it is important to emphasize that in each of these studies of metal ion assisted elimination of mercaptan, the reported yield of mercaptide salt was isolated before the trapping reagent was added to the solution. Indeed, the direct reaction with the isothioureas was tried in some cases for the synthesis of the final products and, in each case, more stringent reaction conditions (higher temperatures, sealed tubes) were required to obtain reasonable yields.

TABLE II

RESULTS OF ELIMINATION AND TRAPPING EXPERIMENTS[a]

Isothiourea	Mercaptide salt (yield, %)[b]	Trapping reagent	Derivative formed (yield, %)
2a	$AgSCH_3$ (100)	NH_3	1-Phenyl-2-cyanoguanidine (52)
2a	$HgClSCH_3$ (87)	CH_3OH–CH_3O^-	N-Phenyl-N′-cyano-O-methylisourea (46)
2b	$AgSCH_3$ (97)	NH_3	1-Cyclohexyl-2-cyanoguanidine (54)
2c	$AgSCH_3$ (86)	NH_3	1-Ethyl-2-cyanoguanidine (22)
2d	$AgSCH_3$ (100)	$C_6H_{11}NH_2$	1-Cyclohexyl-2-cyanoguanidine (23)
2d	$AgSCH_3$ (96)	NH_3	Dicyandiamide (50)

[a] All reactions were in DMF–Et_3N solutions except the second, which was in CH_3OH–Et_3N. [b] All yields are corrected for the triethylamine salt present.

The thermal elimination of methyl mercaptan from **2a** was also investigated. Heating a solution of **2a** in diphenyl ether to 150° while sweeping the gas evolved through two traps containing aqueous silver nitrate resulted, after 2 hr, in an 80% yield of silver mercaptide being collected. Subsequent addition of ammonium nitrate to the diphenyl ether solution led to the formation of **4** in 32% yield.

Although the intermediates in these reactions could not be isolated in monomeric form and characterized, despite numerous attempts to do so,[7] the evidence presented uniquely supports N-cyanocarbodiimides as the reactive species. It is known that many carbodiimides with unsaturated substituents on nitrogen are short-lived in monomeric form.[8] It would appear that N-cyanocarbodiimides are no exception to this, although they may be relatively stable in inert solvents at low concentrations.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were recorded on a Varian HA-60-EL spectrometer using tetramethylsilane as an internal standard (τ 10.0) and solvents as specified. Ir spectra were recorded on Perkin-Elmer Model 137B and Beckman Model IR-8 spectrophotometers.

Synthesis of N-Substituted N′-Cyano-S-methylisothioureas.—The preparations of **2a–2d** were modeled after the procedure reported by Davidson.[9] The products were identified by comparison of melting points with those reported in the literature,[10] by elemental analyses (correct to within ±0.3% for each element

(7) In a few experiments it was possible to obtain ir spectra of the filtrate after removal of the metal mercaptide and some of the DMF solvent. The carbodiimide region (2200–2000 cm^{-1}) showed an absorption band at *ca.* 2150 cm^{-1} which was not due to solvent or C≡N of starting material. This band disappeared as further solvent was removed and was always absent in the red oils or glasses resulting from complete removal of solvent.

(8) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

(9) J. S. Davidson, *Chem. Ind.* (London), **48**, 1977 (1965).

(10) F. H. Curd, J. A. Henry, T. S. Kenny, A. G. Murray, and F. L. Rose, *J. Chem. Soc.*, 1630 (1948).

in each case), and by their ir (Table I) and nmr spectra. The procedure for **2a** is given as a typical example.

N-Phenyl-N′-cyano-S-methylisothiourea (2a).—Dimethyl cyanodithioimidocarbonate[6] (10.0 g, 0.069 mol) was dissolved in 200 ml of ethanol. To the stirred solution was added 10 ml (0.11 mol) of aniline over a period of 30 min. The solution was kept at 80° for 5 hr and then reduced by evaporation to one-fourth the original volume. The white crystals which appeared while the solution was cooled at 0° for 2 hr were collected by filtration. Recrystallization from ethanol gave 11.0 g (83%) of white crystals: mp 194–196° (lit.[10] mp 195–196°); ir (KBr) 3210 (NH), 2160 and 2180 (shoulder) (C≡N), and 1520 cm^{-1} (C=N); nmr (DMSO-d_6) τ 0.05 (s, 1, NH), 2.4–2.9 (m, 5, C_6H_5), and 7.45 (s, 3, CH_3S).

Anal. Calcd for $C_9H_9N_3S$: C, 56.5; H, 4.70; N, 22.0; S, 16.7. Found: C, 56.5; H, 4.65; N, 21.9; S, 16.7.

1-Phenyl-2-cyanoguanidine from 2a. Method A.—A solution of 0.27 g (0.0016 mol) of silver nitrate in 20 ml of DMF was added to a solution of 0.30 g (0.0016 mol) of **2a** and 10 drops of triethylamine in 50 ml of DMF. A yellow precipitate of silver mercaptide formed immediately. After the mixture was stirred for 1 hr at room temperature and then cooled in a Dry Ice–acetone bath, the yellow precipitate was collected by filtration and washed with DMF. After drying it amounted to 0.235 g, a quantitative yield of silver mercaptide. Ammonia was bubbled through the filtrate for 1 hr at 0°. The mixture was then stirred at room temperature for several hours followed by removal of all but 10 ml of the DMF by vacuum distillation. Addition of 100 ml of ether and cooling in a Dry Ice–acetone bath led to the formation of 0.13 g (52%) of 1-phenyl-2-cyanoguanidine, mp 197–199° (lit.[11] mp 195–196°). The ir and nmr spectra were consistent with the proposed product, as was the microanalysis (below).

Anal. Calcd for $C_8H_8N_4$: C, 60.0; H, 5.00; N, 35.0. Found: C, 60.3; H, 5.11; N, 35.2.

Method B.—The thermal elimination of methyl mercaptan from **2a** was effected by heating a solution of 1.00 g(0.0053 mol) of **2a** in 100 ml of diphenyl ether for 2 hr at 150° while nitrogen gas swept the mercaptan into traps containing 5% aqueous silver nitrate solution. The silver mercaptide collected after 2 hr was 0.65 g or 79.5% of the theoretical amount. At this point 1.00 g (0.013 mol) of ammonium nitrate was added to the diphenyl ether solution and the temperature was held at 120° for 12 hr. The solvent was removed by vacuum distillation, leaving a red oil from which a white solid formed after a few hours. Purification of the solid by column chromatography (neutral alumina) afforded 0.27 g (32.2%) of white solid, mp 197–198°, ir and nmr spectra identical with those of the product from method A.

N-Phenyl-N′-cyano-O-methylisourea from 2a.—To a stirred solution of 1.00 g (0.0053 mol) of **2a** and 1 ml of triethylamine in 150 ml of absolute methanol at 50° was added 1.25 g (0.0062 mol) of mercuric chloride. A white precipitate formed immediately. After the reaction mixture was stirred at room temperature for 45 min, the precipitate of $HgClSCH_3$ was collected by filtration, yield 1.29 g (87%). Sodium methoxide (0.070 g, 0.0013 mol) was then added to the colorless filtrate as a catalyst and stirring was continued at 50° for 10 hr. Removal of solvent by distillation gave 0.425 g (46%) of long, white needles: mp 166–167°; nmr (DMSO-d_6) τ −0.3 (s, 1, NH), 2.4–2.7 (m, 5, C_6H_5), and 6.1 (s, 3, CH_3O).

Anal. Calcd for $C_9H_9N_3O$: C, 61.7; H, 5.14; N, 24.0. Found: C, 61.6; H, 5.03; N, 24.1.

1-Cyclohexyl-2-cyanoguanidine from 2b.—To a solution of 0.31 g (0.0016 mol) of **2b** and 1 ml of triethylamine in 50 ml of DMF was added a solution of 0.27 g (0.0016 mol) of silver nitrate in 20 ml of DMF. The yellow precipitate of silver mercaptide formed immediately and was removed by filtration after the solution had been stirred for 2 hr. The yield of silver salt was 0.226 g (97%). Dry ammonia was bubbled through the filtrate for 1 hr at 0° and then the mixture was stirred for 10 hr at room temperature. After the DMF solution was concentrated to 10 ml by vacuum distillation, it was diluted with ether and water and allowed to stand for 2 days. The crystals which formed during this time were collected and found to constitute a 54% yield: mp 157–158° (lit.[11] mp 158–160°); nmr (DMSO-d_6) τ 3.1–3.8 (m, 3, NH_2 and $C_6H_{11}NH$) and 8.0–9.0 (m, 11, C_6H_{11}).

Anal. Calcd for $C_8H_{14}N_4$: C, 57.8; H, 8.44; N, 33.8. Found: C, 58.1; H, 8.42; N, 33.8.

(11) B. C. Redmon and D. E. Nagy, U. S. Patent 2,455,807 (1948).

1-Ethyl-2-cyanoguanidine from 2c.—A solution of 0.255 g (0.0016 mol) of **2c** and 1 ml of triethylamine in 50 ml of DMF was combined with a solution of 0.27 g (0.0016 mol) of silver nitrate in 20 ml of DMF. After the resulting solution was stirred for 1 hr the precipitated silver mercaptide was collected, yield 0.200 g (86%). Dry ammonia was bubbled through the solution for 30 min and then stirring at 40° was maintained for 24 hr. Removal of the solvent by vacuum distillation left a red oil, which was further purified by column chromatography (neutral alumina). Collection of the band eluted with a 1:1 ethyl–cyclohexane mixture yielded a red oil, which could not be induced to crystallize despite repeated attempts. This oil amounted to 0.042 g (22%) and gave spectral and analytical results expected for the desired product: nmr (DMSO-d_6) τ 3.0–3.6 (m, 3, NH_2 and C_2H_5NH), 6.7–7.1 (q, 2, CH_3CH_2), and 8.8–9.1 (t, 3, CH_3CH_2).

Anal. Calcd for $C_4H_8N_4$: C, 42.8; H, 7.20; N, 50.0. Found: C, 42.7; H, 7.26; N, 50.0.

1-Cyclohexyl-2-cyanoguanidine from 2d.—To a stirred solution of 1.00 g (0.0087 mol) of **2d** and 2 ml of triethylamine in 100 ml of DMF was added 1.60 g (0.0094 mol) of silver nitrate in 50 ml of DMF. A light yellow solid precipitated and the solution was stirred for 45 min at 0°. An excess (2 ml) of cyclohexylamine was added to the filtrate after the removal of the silver mercaptide (1.37 g, 100%) and then the mixture was kept at reflux temperature for 6 hr. Vacuum distillation of solvent left a red oil, which was placed on a column of neutral alumina for further purification. The total yield of crystals from the 1:1 ether–chloroform fraction was 0.33 g (23%), mp 157–159° (lit.[11] mp 158–160°). A mixture melting point with the material previously described from **2b** and a consistent ir spectrum were taken as evidence for the product being 1-cyclohexyl-2-cyanoguanidine.

Dicyandiamide from 2d.—A solution of 1.00 g (0.0087 mol) of **2d** and 1 ml of triethylamine in 100 ml of DMF was stirred for 45 min with 1.60 g (0.0094 mol) of silver nitrate. The yellow silver mercaptide (1.3 g, 96%) was removed by filtration and then dry ammonia was passed through the filtrate for 1 hr at 0°. Concentration of the solution to 20 ml by vacuum distillation followed by cooling in a Dry Ice–acetone bath produced 0.46 g of white solid. Recrystallization from ethanol gave 0.40 g (50%) of white crystals, mp 208–209° (lit.[12] mp 209–211°). The ir spectrum matched the recorded spectra of dicyandiamide.[13]

Registry No.—**2a**, 21504-96-1; **2b**, 24010-75-1; **2c**, 5848-25-9; **2d**, 15760-26-6; methyl mercaptan, 74-93-1; N-phenyl-N′-cyano-O-methylisourea, 24010-78-4; 1-cyclohexyl-2-cyanoguanidine, 24010-79-5; 1-ethyl-2-cyanoguanidine, 24010-80-8.

(12) "Handbook of Chemistry and Physics," 46th ed, Chemical Rubber Co., Cleveland, Ohio, p C-954.

(13) "Sadtler Standard Spectra," Sadtler Research Laboratories, Inc., Spectra No. 497 and 13632.

Evidence for an Azomethine Ylide Intermediate in the Carbonyl-Assisted Decarboxylation of Sarcosine. A Novel Synthesis of *dl*-Phenylephrine Hydrochloride

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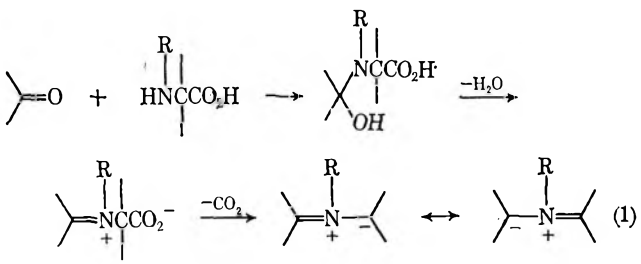
There is much evidence to indicate that the rate of thermal decarboxylation of α-amino acids is accelerated in the presence of certain aromatic carbonyl compounds.[1] For cases involving amino acids with primary amino groups, the effect has been interpreted mecha-

(1) A. F. Al-Sayyab and A. Lawson, *J. Chem. Soc., C*, 406 (1968), and references cited therein.

nistically.[2] Related N-alkyl α-amino acids also undergo carbonyl-assisted decarboxylation.[3] No attempt has been made, however, to explain their behavior mechanistically. The mechanisms which apply to ordinary unsubstituted amino acids cannot be applied to N-alkyl derivatives, since dehydration of initially formed carbinols (eq 1) must at least formally lead to



(1)

dipolar intermediates instead of the usual α-imino acids. The loss of carbon dioxide from betaines such as those shown offered the intriguing possibility of forming a resonance-stabilized azomethine ylide.[4] In this note we wish to report chemical evidence for this type of ylide intermediate in reactions of sarcosine (N-methylglycine) with benzophenone and benzaldehyde.

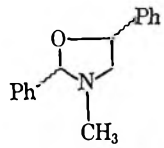
Results

When sarcosine was heated in a melt of benzophenone at 170° it dissolved slowly with concomitant loss of carbon dioxide and dimethylamine. Extraction of an ether solution of the cooled melt with dilute HCl yielded an oily, basic fraction from which 2,2,5,5-tetraphenyl-3-methyloxazolidine (**1**) and 1,1-diphenyl-2-methylaminoethanol (**2**) were isolated by fractional crystallization. The infrared spectrum of **1** showed typical N-methyl absorption at 3.55 μ. Its nmr spectrum indicated aromatic, methylene, and methyl protons in the predicted ratio of 20:2:3. The structure of **1** was confirmed by hydrolysis to form **2**. Compound **2** exhibited broad infrared absorption at 2.92 μ attributable to both OH and NH functionality. Nmr indicated the expected ratio of aromatic, methylene, and methyl protons (10:2:3). Acetylation of **2** with acetic anhydride in pyridine gave a crystalline N-acetyl derivative **3**, whose nmr spectrum indicated a new methyl signal at δ 2.00 with peak area equal to that under the N-methyl peak. The ir spectrum of **3** showed strong absorption at 6.15 μ characteristic of *N,N-dialkylamides*. When **3** was refluxed in toluene in the presence of *p*-toluenesulfonic acid, dehydration occurred to form N-acetyl-N-methyl-2,2-diphenylvinylamine (**4**) in high yield. The highly conjugated nature of **4** was clearly evidenced by strong ultraviolet absorption at 228 and 278 nm (ε 18,200 and 13,700, respectively).

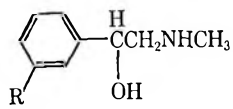
We concluded that **2** must have been formed by hydrolysis of **1** during work-up, since **2** did not react with benzophenone to form **1** under decarboxylation conditions and because no **2** was detected in crude sarcosine reaction mixtures by thin layer chromatography.

Acetylation of the crude sarcosine–benzophenone decarboxylation product followed by silica gel column chromatography led to the isolation of N-diphenylmethyl-N-methylacetamide (**6**). The amide had physical properties identical with those of an authentic specimen prepared by methylating N-acetylbenzhydrylamine. The isolation of **6** showed that N-methylbenzhydrylamine (**5**) must have been present in the original basic extract.

When sarcosine was heated in benzaldehyde, decarboxylation and formation of dimethylamine readily occurred at 150–170°. Fractional distillation of the reaction mixture gave a single, distillable product which was shown to be 2,5-diphenyl-3-methyloxazolidine (**7**) (27% yield). As in the case of **1**, compound **7** exhibited



7



8a, R = H
b, R = OCH_2Ph
c, R = OH (hydrochloride)

ir absorption at 3.55 μ characteristic of an N-methyl compound. The probable presence of *cis* and *trans* isomers made interpretation of the nmr spectrum difficult; however, the expected ratio of aromatic, methylene, and methyl protons was observed (10:2:3). Hydrolysis of **7** produced benzaldehyde and 2-methylamino-1-phenylethanol (**8a**) in 72 and 94% yields, respectively. When **8a** was heated in benzaldehyde under decarboxylation conditions, **7** was formed in 52% yield, suggesting that **8a** might actually have been a reaction intermediate. However, since no **8a** was detected in the crude decarboxylation product by thin layer chromatography prior to distillation, the hypothesis was not confirmed.

Comparable yields of **7** were formed when 2 equiv of benzaldehyde and 1 equiv of sarcosine were refluxed for several hours in benzene. This modification of the benzaldehyde reaction ultimately led to a novel synthesis of *dl*-phenylephrine hydrochloride (**8c**). Sarcosine and 3-benzyloxybenzaldehyde reacted in refluxing xylene to form (after hydrolysis) 1-(3-benzyloxyphenyl)-2-methylaminoethanol (**8b**) in 23% yield. Hydrogenolysis of **8b** in methanolic HCl then gave **8c** in nearly quantitative yield.

Discussion

The array of products observed when sarcosine was decarboxylated in benzophenone suggested the reaction sequence involving a resonance-stabilized azomethine ylide, shown in Scheme I.[5] Azomethine ylides have been reported previously;[6,7] however, none appears to have been observed in the course of amino acid decomposition. The formation of dimethylamine

(2) F. G. Baddar, *J. Chem. Soc.*, S163 (1949).

(3) G. Chatelus, *Bull. Soc., Chim. Fr.*, 2523 (1964). S. Akabori and K. Momotani, *J. Chem. Soc. Jap.*, **64**, *608 (1943)*; *Chem. Abstr.*, **41**, *3774* (1947). E. Takagi, *J. Pharm. Soc. Jap.*, **71**, 648 (1951); *Chem. Abstr.*, **46**, 8045 (1952); and subsequent papers by the latter author.

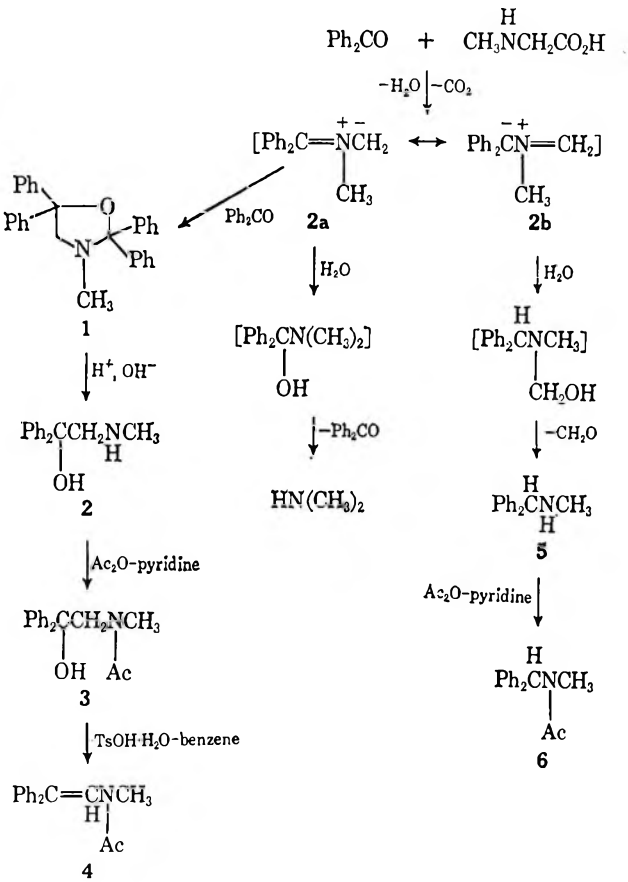
(4) Recently an ylide mechanism was proposed for the thermal decarboxylation of N-carboxymethylpyridinium bromide: W. G. Phillips and K. W. Ratts, *Tetrahedron Lett.*, **18**, 1383 (1969).

(5) Our results do not completely exclude the possibility that condensation of the intermediate betaine may have taken place prior to decarboxylation (*cf.* ref 4); however, we favor the mechanism shown in Scheme I because it also explains the facile formation of dimethylamine in all cases.

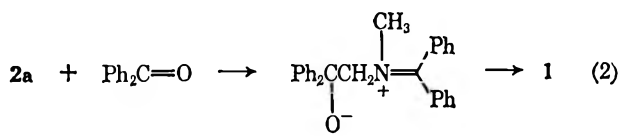
(6) R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, **2**, 565 (1963).

(7) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

SCHEME I

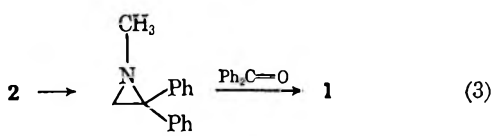


and **5** are explained in terms of hydrolysis of the ylide. Addition of water to the ylide probably leads to unstable amino alcohols, which readily collapse to form products. Compound **5** is of special interest, since it corresponds to the "transamination" products frequently encountered in carbonyl-assisted decarboxylations of α-amino acids. We envisage two possible routes for the formation of **1**. Like other dipolar species[6] **2a** may have undergone cycloaddition to excess ketone present (eq 2). The dipolar addition product

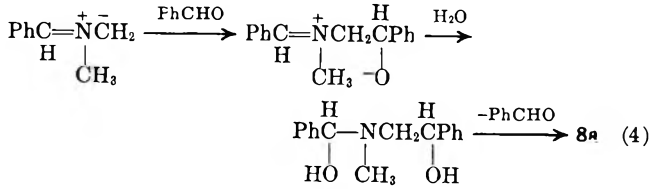


of **2b** and benzophenone (4,4,5,5-tetraphenyl-3-methyloxazolidine) was not isolated in the present work.

Alternatively, the ylide may have first collapsed to a valence-bond tautomeric aziridine[7] and subsequently reacted further[8] (eq 3). It seems likely that a similar



mechanism was operative in reactions of sarcosine and benzaldehyde. As mentioned earlier, since **8a** reacted with benzaldehyde to form **7**, the possibility remains that **8a** is actually a reaction intermediate. If this is the case it is possible to explain the formation of **8a** in terms of the well-known Hammick reaction[9] (eq 4).



Experimental Section[10]

Decarboxylation of Sarcosine in Benzophenone.—A mixture of sarcosine (1.79 g, 0.020 mol) and benzophenone (25 g) was heated to 150° for 2 hr and to 170° for another 2 hr. The heterogeneous melt rapidly evolved CO_2 and dimethylamine at 170°.[11] On cooling ether was added and the resulting solution was decanted from a small amount of gummy material. Extraction of the ether solution with 4 *N* HCl followed by neutralization with 6 *N* NaOH gave 0.89 g of yellow oil, which partially crystallized on treatment with ethanol at 0° to yield 0.10 g (1.3%) of **1**: mp 150.5–152°; 100-MHz nmr δ 2.04 (s, 3 H, $CH_3N<$), 3.73 (s, 2 H, CH_2), and 6.7–7.9 ppm (m, 2 H, aromatic protons); ir (KBr) 3.55 μ (NCH_3).

Anal. Calcd for $C_{28}H_{25}NO$: C, 85.90; H, 6.44; N, 3.58. Found: C, 85.5; H, 6.4; N, 3.4.

In a similar experiment prolonged cooling of the ethanolic solution yielded a second crystalline product (*ca.* 2 g) which was filtered, washed with ethanol, dried, and showed to be crude **2** by comparing ir and nmr data with those of authentic **2** described below. Part of **2** (1.537 g) was dissolved in dry pyridine (25 ml) and treated with acetic anhydride (2 ml). After 1.5 hr at 25° water was added and the mixture was extracted with ether. Concentration of the dried ($MgSO_4$) ether solution gave 1.65 g of white solid. Recrystallization from benzene–hexane yielded 0.503 g of **3**: mp 138.5–140°; 100-MHz nmr δ 2.00 (s, 3 H, CH_3CO), 2.42 (s, 3 H, CH_3N), 4.19 (s, 2 H, CH_2), 5.90 (s, 1 H, OH), and 7.08–7.60 ppm (m, 10 H, aromatic protons); ir (KBr) 3.05 (OH) and 6.15 μ (C=O, broad, partially split).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.2; H, 7.2; N, 5.1.

In a similar experiment starting with sarcosine (0.0506 mol) and benzophenone (25 g), 1.221 g of crude basic products were obtained. Acetylation gave 0.996 g of neutral products, which on trituration with ether afforded 0.409 g of **3**, mp 136–138.5°. The oil obtained after trituration (0.587 g) was chromatographed over 30 g of silica gel (28–200 mesh, B. Preiser and Co., grade 12). The column was eluted with mixtures of hexane, benzene, and ether. Elution with 50:50–20:80 hexane–benzene gave 0.106 g of **1**. Pure benzene gave *ca.* 0.2 g of benzophenone mixed with a trace of **1**. Further elution with increasing amounts of ether in benzene gave 0.248 g of an unseparated mixture of **3** and **6** (*ca.* 1:1 ratio). Fractions richest in **6** were pooled and rechromatographed over silica gel. Slow elution with 1–15% ether in benzene gave a pure sample of **6** whose solution, ir, and nmr spectra were identical with those of authentic **6**.

Hydrolysis of 3.—A mixture of **3** (1.23 g), mp 137–139°, reagent grade KOH (2.17 g), and redistilled 1-butanol (20 ml) was refluxed under N_2 for 3 hr. Butanol was distilled under

(8) Simple aziridines react with ketones to yield oxazolidines; *cf.* R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed, Interscience Publishers, New York, N. Y., 1967, p 10.

(9) D. L. Hammick, *et al.*, *J. Chem. Soc.*, 3825 (1953).

(10) Melting points were determined on a Thomas–Hoover capillary apparatus and are not corrected. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 21 instrument unless otherwise noted. Nmr spectra were obtained with Varian Associates HA-60 or HA-100 spectrometers in $CDCl_3$ using tetramethylsilane (TMS) as internal reference. Chemical shifts are expressed in parts per million (δ) downfield from TMS. Multiplicity is indicated by letters, where s = singlet, t = triplet, and m = complex, unresolved multiplet. Microanalyses were performed by Mr. T. Atanovich and associates of this laboratory and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(11) The CO_2 was trapped as $BaCO_3$ (88% yield in the case of $Ph_2C{=}O$). Dimethylamine was trapped in aqueous HCl and identified as the hydrochloride by the method of J. Hrdlicka and G. Janicek [*Nature*, **201**, 1223 (1964)]; the bulk of the sarcosine nitrogen appeared to have been expelled in the form of dimethylamine. No attempt was made to identify formaldehyde among the gaseous reaction products.

reduced pressure, leaving an oil which was treated with dilute HCl and extracted with ether. Basification of the acid solution (NaOH) and reextraction with ether gave, after drying (Na_2SO_4) and concentration, 0.972 g of crude **2** as a viscous oil. The amino alcohol was purified *via* the hydrochloride. Dissolution of the crude product in dilute HCl followed by evaporation of excess water and HCl under reduced pressure gave 1.088 g (90%) of **2** HCl, mp 218–219° dec. Recrystallization from 2-propanol gave colorless microneedles, mp 217.5–219° dec.

Anal. Calcd for $C_{15}H_{18}NOCl$: C, 68.3; H, 6.8; Cl, 13.5; N, 5.3. Found: C, 68.3; H, 6.9; Cl, 13.6; N, 5.2.

A solution of the hydrochloride (0.396 g) in water (10 ml) was basified by dropwise addition of concentrated NH_4OH. An oil separated, which crystallized completely after several hours at 0°, yield 0.279 g (82%). Repeated recrystallizations from aqueous ethanol gave colorless needles of **2**: mp 80–115° (apparently polymorphic); 60-MHz nmr δ 2.47 (s, 3 H, NCH_3), 2.75 (s, 2 H, OH and NH), 3.34 (s, 2 H, NCH_2), and 6.98–7.64 ppm (m, 10 H, aromatic protons); ir (KBr) 2.92 (OH and NH), 3.57 (NCH_3, weak), 6.16 (CN), 6.28 (aromatic C=C), and 9.52 μ (CO).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.4; H, 7.4; N, 6.2.

Hydrolysis of 1.—A mixture of **1** (0.146 g), mp 149.5–151°, and 1 *N* HCl (10 ml) was refluxed under N_2 for 2.25 hr. The cooled reaction mixture was extracted with ether to remove benzophenone and the clear, aqueous phase was concentrated under reduced pressure to yield 0.097 g (99%) of **2** HCl, mp 207–209°. The identity of the product was confirmed by its ir spectrum.

Dehydration of 3.—A solution of the amido alcohol **3** (0.235 g), mp 138.5–140°, in toluene (10 ml) was treated with *p*-toluenesulfonic acid monohydrate (0.064 g) and refluxed for 1 hr under N_2. The toluene solution was diluted with ether, washed with $NaHCO_3$ solution, dried, and concentrated to yield 0.199 g of pale yellow oil which slowly crystallized at 25°. The crude product was chromatographed over 20 g of 40–200 mesh silica gel. Elution with benzene and 10% ether in benzene yielded a small amount of an unidentified, nonpolar by-product. Further elution with 20% ether in benzene gave 0.180 g (82%) of **4** as colorless crystals. Recrystallization from ether–hexane yielded prisms of pure **4**: mp 85–86.5°; 60-MHz nmr δ 2.15 (s, 3 H, CH_3CO), 2.78 (s, 3 H, $CH_3N<$), 6.74 (s, 1 H, HC=), and 7.08–7.58 ppm (m, 10 H, aromatic protons); ir (KBr) 5.91 (C=O), 6.12 (C=C), and 11.55 μ [–CH=C– (ν CH)]; uv max (ethanol) 228 (ϵ 18,200) and 278 nm (ϵ 13,800).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.6; H, 6.7; N, 5.4.

N-Diphenylmethyl-N-methylacetamide (6).—A solution of N-acetylbenzhydrylamine[12] (2.184 g, 0.00973 mol), mp 148–149°, in distilled diglyme (30 ml) was treated with 0.466 g (0.0109 mol) of 56% NaH (suspension in mineral oil, Metal Hydrides, Inc., Beverly, Mass.). The mixture was stirred at 65° under a nitrogen atmosphere for 25 min and cooled to 25°, and a solution of dimethyl sulfate (1 ml) in diglyme (4 ml) was added. After 16.5 hr at 65° water was added and the mixture was extracted with ether. Concentration of the dried ($MgSO_4$) ether solution gave an oil, which was shown by thin layer chromatography to contain a 1:1 mixture of starting material and a single new product. The oil was redissolved in diglyme (30 ml) and treated with NaH and dimethyl sulfate as previously described. After alkylation had been allowed to proceed for 48 hr at 65°, the mixture was worked up as before to yield a partially crystalline product. Pressing the crystals between layers of filter paper gave 1.64 g (71%) of **6**, mp 81–82°. Recrystallization from aqueous methanol gave 1.62 g of colorless prisms: mp 81–82° (corrected) (lit.[13] mp 80–83°); 100-MHz nmr δ 2.16 (s, 3 H, CH_3CO), 2.68 and 2.74 (two s, 3 H total area, rotamers of $CH_3N<$, peak at 2.68 disappeared at 55°), 6.15 (s, 1 H, CH), and 6.60–7.80 ppm (m, 10 H, aromatic protons); ir ($CHCl_3$)[14] 3.34, 6.06 (C=O), 6.90, 7.00, 7.14, 7.55, 7.65, 8.86, 9.28, 9.70, and 9.90 μ.

Decarboxylation of Sarcosine in Benzaldehyde.—A 100-ml, round-bottomed flask arranged for simple distillation was charged with sarcosine (10.0 g, 0.112 mol) and reagent grade benzaldehyde (50 ml). Upon heating with stirring at 170° the sarcosine dissolved rapidly with concomitant evolution of carbon dioxide and dimethylamine.[11] After 3 hr the clear yellow solution was cooled to 25°, diluted with ether (200 ml), and extracted with saturated, aqueous Na_2CO_3. Ether and benzaldehyde were removed on a rotary film evaporator to yield an oil, which was fractionated through a 3-in. Vigreux column. Following a negligible forerun 7.28 g (27%) of **7** was collected, bp 130–150° (0.1 mm). A viscous pot residue remained which could not be distilled at 280° (oil-bath temperature). A sample of the clear distillate, bp 132° (0.1 mm), showed the following properties: 100-MHz nmr δ 2.04 (s, 3 H, CH_3N), 3.73 (s, 2 H, CH_2), and 6.7–7.9 ppm (m, 10 H, aromatic protons); ir (liquid film) 3.55 μ (NCH_3).

Anal. Calcd for $C_{15}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.6; H, 6.9; N, 5.9.

A solution of the oxazolidine **7** (1.568 g) in 4 *N* HCl (10 ml) was stirred for 1.75 hr at 25° and extracted with ether, and the ether extract was concentrated. Treatment with an excess of 2,4-dinitrophenylhydrazine reagent (H_2SO_4) gave 1.354 g (72%) of benzaldehyde 2,4-dinitrophenylhydrazone, mp 233–234.5°. The aqueous phase from the ether extraction was concentrated to a syrup and neutralized with aqueous Na_2CO_3 solution. Extraction with ether followed by drying the extract (Na_2SO_4) and concentration under reduced pressure gave 0.935 g (94%) of crystalline **8a**. Recrystallization from ether yielded a pure specimen: mp 75.5–76.5° (lit.[15] mp 75.5–76°); 100-MHz nmr δ 2.38 (s, 3 H, CH_3N), 2.60–2.88 (unresolved group of peaks, 4 H, NH, OH, and CH_2), 4.66 (q, 1 H, >CHOH), and 7.25 ppm (s, 5 H, aromatic protons).

Reaction of 8a with Benzaldehyde.—A sample of the amino alcohol **8a** (0.148 g), mp 74–75°, was heated with benzaldehyde (1 ml) for 3 hr at 170° under a nitrogen atmosphere. On cooling, glpc analysis on a 10 ft × 0.25 in. column containing 5% DC-200 on 60–80 mesh siliconized Chromosorb W (120°) showed that **7** had been formed in 52% yield (0.076 g of hexadecane served as internal standard). The identity of **7** was confirmed by trapping a sample from the effluent He stream and comparing corresponding ir spectra.

***dl*-Phenylephrine.**—A 100-ml, round-bottomed flask arranged with a Dean–Stark water trap was charged with sarcosine (0.897 g, 0.0101 mol), 3-benzyloxybenzaldehyde[16] (4.24 g, 0.020 mol), and xylene (50 ml). After refluxing 0.2 hr practically all the sarcosine had disappeared and water (*ca.* 0.2 ml) was collected. The pale yellow xylene solution was diluted with ether (100 ml), 4 *N* HCl (20 ml) was added, and the mixture was stirred vigorously at 25° for 20 hr. The xylene was separated and the aqueous HCl was concentrated under reduced pressure to yield a crystalline residue. The crystals were dissolved in water (10 ml), 3 *N* NaOH (10 ml) was added, and the final mixture was extracted with ether. The ether extract was washed with saturated brine, dried (Na_2SO_4), and concentrated under reduced pressure to yield 0.603 g (23%) of crude **8b**, mp 87–95°. Recrystallization from ethyl acetate gave colorless crystals, mp 102.5–103.5° (lit.[17] mp 103°).

A solution of **8b** (0.267 g), mp 101–102.5°, in methanol (3 ml) was added to 10% Pd on charcoal (0.075 g, prereduced with hydrogen) in a mixture of methanol (20 ml) and concentrated HCl (1 ml). Hydrogenolysis with H_2 at 1 atm was complete after 2.5 hr. Evaporation of the solvent and HCl gave crude **8c** in quantitative yield. Recrystallization from ethanol gave colorless prisms, mp 143–146.5° dec (lit.[18] mp 140–145° dec).

Registry No.—Sarcosine, 107-97-1; **1**, 24010-81-9; **2**, 24010-82-0; **2** hydrochloride, 24010-83-1; **3**, 21901-77-9; **4**, 24010-85-3; **6**, 24010-86-4; **7**, 24010-87-5; **8a**, 6589-55-5; **8c**, 20368-45-0.

Acknowledgment.—The author wishes to thank Mr. James Schaefer for the excellent technical assistance he provided throughout the course of this work.

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(13) H. Dahn and U. Solms, *Helv. Chim. Acta*, **35**, 1162 (1952).

(14) A Perkin-Elmer Model 137 spectrophotometer was used.

(15) A. Terada, *Nippon Kagaku Zasshi*, **81**, 759 (1960); *Chem. Abstr.*, **56**, 370 (1962).

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(17) A. Z. Britten, *Chem. Ind.* (London), 771 (1968). A correct elemental analysis was obtained for our material. The yield of analytically pure **8b** was increased to *ca.* 50% when the reaction was carried out in refluxing benzene for 16 hr.

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The Reaction of 5-Ethylidenebicyclo[2.2.1]hept-2-ene with Chlorosulfonyl Isocyanate[1]

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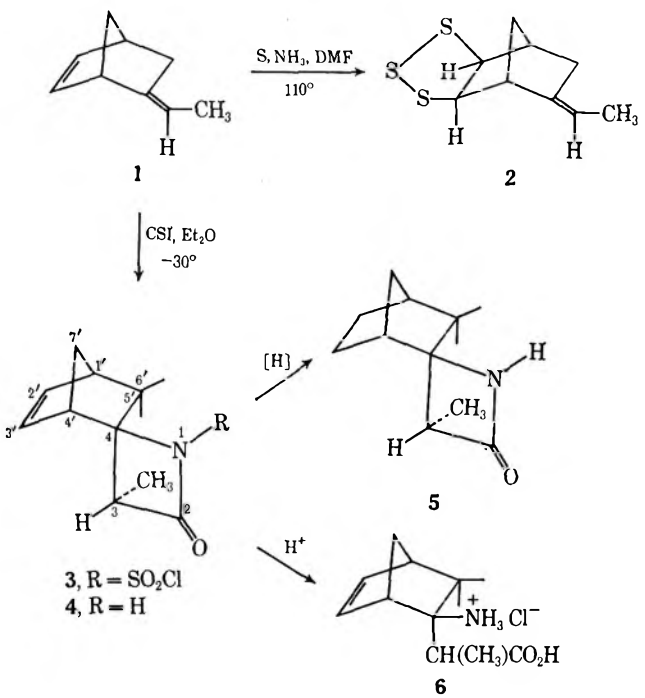
The high yield and selective and stereospecific "active" sulfuration of norbornene and 5-ethylidenebicyclo[2.2.1]hept-2-ene (**1**) to give *exo*-3,4,5-trithiatricyclo[5.2.1.$0^{2,6}$]decane and its 8-ethylidine derivative (**2**), respectively, has recently been reported.[3] Since this new reaction may well proceed *via* an ionic mechanism,[4] it is significant that in these and other norbornyl olefins and diolefins, sulfur adds exclusively to the norbornenyl ring double bond.

Since we too had noted such exclusivity in the cycloaddition reactions of chlorosulfonyl isocyanate (CSI) with bridged bi- and tricyclic olefins,[5] we wish to report an unusual divergence from this now expected pathway in the reaction of CSI with **1**.

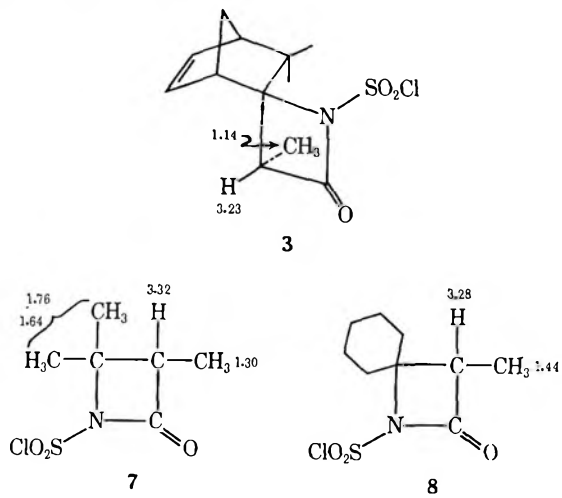


1 2 5 6

Thus, treatment of **1** with electrophilic CSI led in 85% yield to the single β-lactam, 1-chlorosulfonyl-3-methyl-2-azetidinone-4-spiro-5′-bicyclo[2.2.1]hept-2′-ene (**3**), in which exclusive attack had occurred at the exocyclic double bond. In the nmr, the two vinyl protons in **3** appeared as coupled doublets at δ 6.40 and 6.08. The Markovnikov orientation of cycloaddition **3** was determined by the location in the nmr of methine and methyl protons. Sufficient N-chlorosulfonyl-β-lactams have been prepared to provide chemical shift data for such protons on C atoms adjacent to N and/or C=O functions of the azetidinone ring. A comparison of the relevant nmr data for two of these reference compounds, 1-chlorosulfonyl-3,4,4-trimethyl-2-azetidinone (**7**),[6] 1-chlorosulfonyl-3-methyl-1-azaspiro[3.5]nonan-2-one (**8**),[6] and **3** are summarized in Chart I. Finally, the stereochemistry of **3** is based

CHART I

NMR DATA FOR N-CHLOROSULFONYL-β-LACTAMS. CHEMICAL SHIFTS (δ) ARE INDICATED FOR METHYL AND METHINE PROTONS



on the precedented attack of CSI at the exo face of norbornyl olefins[5] and the observed stereospecificity of such cycloadditions to olefins.[7,8]

The strained electron-deficient carbonyl group in **3** appeared at 5.48 μ in the infrared as well as the expected SO_2 bands at 7.06 and 8.43 μ.[5] At room temperature, exposed to the atmosphere, β-lactam **3** decomposed to colored products within hours, while at −20° such decomposition occurred much more slowly. As with norbornadiene- and dicyclopentadiene-CSI adducts, **3** did not react further with CSI, while treatment of **1** with excess CSI led only to **3**.

Removal of the electronegative SO_2Cl function in **3** with thiophenol–pyridine in acetone afforded the unsubstituted β-lactam, 3-methyl-2-azetidinone-4-spiro-5′-bicyclo[2.2.1]hept-2′-ene (**4**), in which all nmr signals were now shifted upfield and the NH proton appeared at δ 7.60. Catalytic reduction of **4** led to the completely saturated tricyclic β-lactam **5** in which the bridgehead protons, no longer allylic, are shifted upfield to δ 2.32 and 2.15. In the infrared, the C=O bands in both **4** and **5** appeared as doublets at 5.66 μ. Hydrolysis of **4** with concentrated hydrochloric acid quantitatively converted it into the amino acid hydrochloride **6**.

The results reported herein add further to the confusing data already available on cycloadditions with norbornenyl systems. Thus, while the electrophile dichlorocarbene adds exclusively to the cyclopentene ring double bond in dicyclopentadiene,[9] CSI adds only

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(2) Graduate Research Assistant (1966–1968) on a grant[1] supported by the NIH; taken entirely from the Ph.D. thesis of C. C. Jalandoni, Fordham University, 1969.

(3) T. C. Shields and A. N. Kurtz, *J. Amer. Chem. Soc.*, **91**, 5415 (1969).

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(7) E. J. Moriconi and J. F. Kelly, *Tetrahedron Lett.*, 1435 (1968).

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(9) L. Ghosez, P. Laroche, and L. Bastens, *Tetrahedron Lett.*, 3795 (1964).

to the norbornenyl ring double bond in the same system;[5] further, while "activated" sulfur adds exclusively to the norbornenyl ring double bond in **1**, CSI adds only to the exocyclic double bond. In this latter reaction, whatever the balance between steric factors (involving the approaching electrophile) and the intrinsic reactivity (of each double bond in **1**), the surprising result discourages even tentative mechanistic speculation without further and more comprehensive experimental data.

Experimental Section

Reaction of 5-Ethylidenebicyclo[2.2.1]hept-2-ene (1)[10] with CSI.—A solution of 5.0 g (0.04 mol) of **1** in 20 ml of absolute ether was cooled to −30° by means of a Dry Ice–ethanol bath. To this was added dropwise a solution of 5.9 g (0.04 mol) of CSI in 15 ml of absolute ether. The mixture was stirred at −30° for 30 min, then warmed to room temperature, and stirred again for an additional 30 min. Approximately half of the solvent was removed by passing a stream of nitrogen through the solution and gentle heating. Cooling at −20° for 6 hr afforded the colorless crude **1-chlorosulfonyl-3-methyl-2-azetidinone-4-spiro-5′-bicyclo[2.2.1]hept-2′-ene (3)**. Recrystallization from pentane yielded 9.4 g (86%) of **3** as fine needles: mp 69–70°; ir (CCl_4) 5.48 (C=O), 7.06 and 8.43 μ (SO_2); nmr ($CDCl_3$) δ 1.14 (d, 3, J = 7.5 Hz, CH_3) 1.80 (m, 2, C-7′ protons), 2.25 (m, 2, C-6′ protons), 3.02–3.33 (m, 3, C-3, -1′, -4′ protons), 6.08 (split doublet, 1, C-2′ proton), 6.40 (split doublet, 1, C-3′ proton).

Anal. Calcd for $C_{10}H_{12}NSO_3Cl$: C, 45.89; H, 4.62; N, 5.35. Found: C, 45.59; H, 4.86; N, 5.26.

Treatment of 1 equiv of **1** with 2 equiv of CSI gave only the monoadduct **3**.

Reduction of 3 with Benzenethiol–Pyridine.—A solution of 0.64 g (0.008 mol) of pyridine in 7 ml of acetone was added slowly to a solution of 1.77 g (0.007 mol) of **3** and 1.49 g (0.014 mol) of benzenethiol in 18 ml of acetone cooled to −30° in a Dry Ice–ethanol bath. After 4 hr, 18 ml of water was added dropwise. Phenyl disulfide precipitated and the mixture was filtered while still cold. The solution was extracted with three 50-ml portions of ether, dried (Na_2SO_4), filtered, and evaporated. The residual oil was extracted with 50 ml of boiling pentane and the extract was cooled to −20° for 24 hr to yield 0.40 g (36%) of **3-methyl-2-azetidinone-4-spiro-5′-bicyclo[2.2.1]hept-2′-ene (4)**: mp 97–98°; ir (CCl_4) 2.94 (free NH), 3.12 (bonded NH), 5.66 μ (C=O, doublet); nmr ($CDCl_3$) δ 1.06 (d, 3, J = 7.5 Hz, CH_3), 1.66 (split singlet, 4, C-6′, -7′ protons), 2.87 (broad complex, 3, C-3, -1′, -4′ protons), 6.03 (split doublet, 1, C-2′ proton), 6.22 (split doublet, 1, C-3′ proton), 7.60 (broad singlet, 1, NH).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.84; H, 8.02; N, 8.44.

The analytical sample was prepared by sublimation at 88–89° (0.25 mm).

Catalytic Hydrogenation of 4.—A solution of 0.76 g (0.005 mol) of **4** in 40 ml of absolute ethanol was hydrogenated (5% Pd–C) at an initial hydrogen pressure of 38 psi in a Parr shaker for 1 hr. The catalyst was filtered and the ethanol was evaporated *in vacuo*. The solid residue was recrystallized twice from pentane to give 0.49 g (65%) of **3-methyl-2-azetidinone-4-spiro-2′-bicyclo-[2.2.1]heptane (5)**: mp 76–77°; ir (CCl_4) 2.95 (NH, free), 3.15 (bonded NH), 5.66 μ (C=O, doublet); nmr ($CDCl_3$) δ 1.18 (d, 3, J = 7.5 Hz, CH_3), 1.45 (broad complex, 8, C-3′, -5′, -6′, -7′ protons), 2.15 (broad singlet, 1, C-4′ proton), 2.32 (broad singlet, 1, C-1′ proton) 3.00 (q, 1, J = 7.5 Hz, C-3 proton) 7.38 (broad singlet, 1, NH).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.61; H, 9.14; N, 8.45.

Hydrolysis of 4 with Hydrochloric Acid.—A 0.30-g (0.002 mol) sample of **4** was dissolved in just enough concentrated HCl to cover the solid material and allowed to stand at room temperature for 2 hr. The thick, transparent paste was dried under vacuum with P_2O_5 giving a white solid. Recrystallization from methanol–ether gave 0.37 g (97%) yield of the amino acid hydrochloride (**6**): mp 245–247° dec; ir (KBr) 3.39 (NH), 5.87 μ (C=O); nmr (D_2O) δ 1.37 (d, 3, J = 7.5 Hz, CH_3) 1.82 (broad singlet, 4, C-6, -7 protons), 2.57 [q, 1, J = 7.5 Hz, −CH(CH_3)COOH], 3.12 (broad singlet, 2, C-1, -4 protons), 6.20 (m, 1, C-2 proton), 6.42 (m, 1, C-3 proton).

Anal. Calcd. for $C_{10}H_{16}NO_2Cl$: C, 55.17; H, 7.41; N, 6.43. Found: C, 54.87; H, 7.25; N, 6.72.

Registry No.—**1**, 16219-75-3; **3**, 24265-81-4; **4**, 24265-82-5; **5**, 24265-83-6; **6**, 24265-84-7; chlorosulfonyl isocyanate, 1189-71-5.

(10) Graciously supplied in research quantities by Union Carbide Corp., Chemicals and Plastics, South Charleston, W. Va. 25303.

5-Tetrazolyl Ylides

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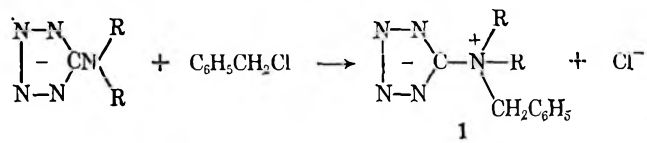
The monoalkylation of a 5-substituted tetrazole, as its anion, normally leads to a mixture of 1- and 2-alkyl-5-substituted tetrazoles; the ratio of isomers is influenced by the nature of the 5 substituent.[1] Even when this substituent is amino or substituted amino, ring alkylation, rather than alkylation on the *exo* nitrogen atom, has been reported to occur preferentially.[2] It has now been found that the monobenzylation of sodium 5-dimethylaminotetrazole in aqueous ethanol gives not only the expected, previously undescribed, 1- and 2-benzyl isomers, poorly soluble in water and readily soluble in benzene, but a third isomer (29% yield), poorly soluble in benzene and soluble in water. The solubility behavior and the high melting point (205° *vs.* 78 and 95°, respectively) suggested the novel ylide **1** (R = CH_3), which would result from benzylation on the *exo* nitrogen. Support



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for this assignment comes from the ^1H nmr spectrum; the signal for methyl protons is shifted to lower field while that for the benzyl methylene protons is shifted to higher field than those observed with either the 1 or 2 isomer (Table I). The chemical-shift values found for the ylides are in the range normally observed for similar quaternary ammonium salts. For example, benzyltrimethylammonium iodide (in Polysol) gives values of τ 6.77 and 5.18 for the methyl and benzyl methylene proton shifts.

The nmr spectrum of the diethyl ylide (**1**, R = C_2H_5) shows the same complex phenyl multiplet observed for the dimethyl compound and the chemical shift of the benzyl methylene protons is nearly the same. Convincing proof of tetrahedral substitution on the exo nitrogen is provided by the 2-Hz splitting of the ethyl

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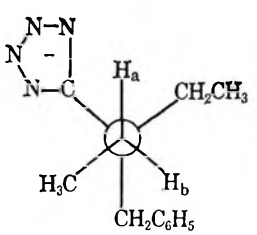
(2) R. A. Henry and W. G. Finnegan, *J. Amer. Chem. Soc.*, **76**, 923 (1954).

TABLE I
NMR CHEMICAL-SHIFT VALUES FOR BENZYLATION PRODUCTS OF 5-DIALKYLAMINOTETRAZOLES

Product[a]	R	Phenyl	Benzyl CH_2	R CH_2	CH_3	Solvent
1-Benzyl	CH_3	2.63	4.37		7.05	DMSO-d_6
		2.66	4.50		7.02	$CDCl_3$
2-Benzyl	CH_3	2.60	4.28		7.06	DMSO-d_6
		2.63	4.43		6.95	$CDCl_3$
exo-N-Benzyl	CH_3	2.72[b]	4.94		6.42	DMSO-d_6
1-(3-Chlorobenzyl)	CH_3	2.6[b]	4.39		7.02	DMSO-d_6
		2.75[b]	4.54		7.10	$CDCl_3$
2-(3-Chlorobenzyl)	CH_3	2.6[b]	4.30		7.05	DMSO-d_6
		2.75[b]	4.47		7.05	$CDCl_3$
exo-N-(3-Chlorobenzyl)	CH_3	2.7[b]	4.93		6.42	DMSO-d_6
1-Benzyl	CH_2CH_3	2.68	4.59	6.77	9.00	$CDCl_3$
2-Benzyl	CH_2CH_3	2.68	4.47	6.53	8.88	$CDCl_3$
exo-N-Benzyl	CH_2CH_3	2.85[b]	4.95	6 09, 6.13[c]	8.70	Polysol[d]

[a] Respective registry numbers follow: 24301-98-2, 24301-99-3, 24302-00-9, 24302-01-0, 24302-02-1, 24302-03-2, 24302-04-3, 24302-05-4, 24302-06-5. [b] Complex multiplet about τ 0.4-0.6 wide. [c] Two overlapping quartets due to intrinsic asymmetry. [d] A proprietary solvent with properties similar to DMSO-d_6 obtained from Stohler Isotope Chemicals, Azusa, Calif.

methylene signal into overlapping quartets. This can only arise from the intrinsic asymmetry of substitution on the nitrogen which leads to chemical nonequivalence of the geminal protons as shown in the projection diagram.



A suspension of **1** (R = CH_3) in a small volume of absolute ethanol at room temperature undergoes no change during several weeks. The addition of an equimolar amount of methyl iodide, however, causes a moderately rapid solution of the ylide; both isomerization to 2-benzyl-5-dimethylaminotetrazole (confirmed by melting point and ir spectrum) and debenzylation to 5-dimethylaminotetrazole occur. Sodium iodide (molar equivalent) also effects a slow isomerization in ethanol (16% in 3 weeks). Isomerization results when the ylides are heated in solution. For example, **1** (R = C_2H_5) is about 50% converted into 2-benzyl-5-diethylaminotetrazole (trace of 1 isomer) after 10 hr in D_2O at 96°, based upon changes in the ^1H nmr spectra with time. When **1** (R = CH_3) is heated at 96° in dimethyl sulfoxide-d_6, 50% of the ylide disappears in 24 hr; however, only about half of this loss corresponds to isomerization, the other half of the ylide having gone to 5-dimethylaminotetrazole (CH_3, τ 7.02) and benzaldehyde (CH, τ −0.10). The latter compound arises from an oxidation of a benzyl group by the solvent since dimethyl sulfide (CD_2H, τ 7.82) also appears. By way of contrast, the 3-chlorobenzyl analog of **1** (R = CH_3) is almost quantitatively converted into the 2 isomer after 2 hr at 96° in dimethyl sulfoxide with no detectable concurrent formation of aldehye and 5-dimethylaminotetrazole.

This isomerization of the ylide resembles the Stevens rearrangement which involves migration of a benzyl group from nitrogen to carbon in quaternary ammonium salt.

Experimental Section

Benzylation of Sodium 5-Dimethylaminotetrazole.—A solution consisting of 33.9 g (0.3 mol) of 5-dimethylaminotetrazole, 120 ml of water, 240 ml of 95% ethanol, 12 g (0.3 mol) of sodium hydroxide, and 38.0 g (0.3 mol) of benzyl chloride was refluxed overnight. After the pH had been readjusted to the phenolphthalein end point, the solution was evaporated to dryness and the solids extracted with one 200-, one 100-, and two 50-ml portions of boiling benzene. Evaporation of the combined benzene extracts left 29.9 g (49%) of mixed 1- and 2-benzyl-5-dimethylaminotetrazoles. Part of the mixture was chromatographed on silica gel–Celite (2:1) using chloroform–benzene (1:1 v/v) to elute first the 2 isomer, then chloroform to remove the 1 isomer;[3] the ratio of the former to the latter was 8:1.

The **2-benzyl-5-dimethylaminotetrazole** was recrystallized from either cyclohexane or benzene: mp 94–95°; uv (95% ethanol) 218 nm (ϵ 4400), 272 (2500).

Anal. Calcd for $C_{10}H_{13}N_5$: C, 59.09; H, 6.45; N, 34.46. Found: C, 59.01; H, 6.44; N, 34.33.

The **1-benzyl-5-dimethylaminotetrazole** was obtained as colorless needles from cyclohexane: mp 77–78°; uv (95% ethanol) 217 nm (ϵ 4350), 239 (3500).

Anal. Calcd for $C_{10}H_{13}N_5$: C, 59.09; H, 6.45; N, 34.46. Found: C, 59.18; H, 6.48; N, 34.40.

The residue remaining after the initial benzene extractions was digested with 400 ml of boiling 2-propanol and filtered. After the crystalline product had been removed from the chilled filtrate, the mother liquors were used again to extract the cake. The yield of crude ylide **1** (R = CH_3) recovered after this operation had been repeated four times was 18.1 g (28.8%): mp 185–195° (recrystallization of a portion from 2-propanol raised the melting point of the fine, felted needles to 204–205°); uv (95% ethanol) 217 nm (ϵ 4500), 258 (330), 263 (460), 270 (410).

Anal. Calcd for $C_{19}H_{13}N_5$: C, 59.09; H, 6.45; N, 34.46. Found: C, 59.16; H, 6.54; N, 34.36.

The 1- and 2-benzyl-5-dialkylaminotetrazoles, as well as the parent 5-dialkylaminotetrazoles, all show a strong absorption in their ir spectra in the range of 1590–1640 cm^{-1}. This absorption is absent with the ylides.

Benzylation of Sodium 5-Diethylaminotetrazole.—A procedure similar to the above was employed except that the dried mixture of products was extracted with cyclohexane rather than benzene. The yield of mixed 1- and 2-benzyl-5-diethylaminotetrazole was 65%; the ratio of isomers was 1:5 based on ^1H nmr. The ylide **1** (R = C_2H_5) was extracted from the cyclohexane-insoluble residue with boiling benzene–2-propanol (85:15) and crystallized slowly when the filtrate was chilled at 5° for several days. Recrystallization from acetone gave large, transparent colorless prisms of a monohydrate, mp 125–130°, with slumping from 110°. The yield was about 13%.

(3) The first material off the column is assigned the 2-isomer structure since such isomers are more soluble and less polar than the corresponding 1 isomers [M. H. Kaufman, F. M. Ernsberger, and W. S. McEwan, *J. Amer. Chem. Soc.*, **78**, 4197 (1956)].

Anal. Calcd for $C_{12}H_{17}N_5 \cdot H_2O$: N, 28.09; H_2O, 7.33. Found: N, 28.16; H_2O, 7.9.

2-Benzyl-5-benzylmethylaminotetrazole.—Benzylation of sodium 5-benzylmethylaminotetrazolate in an analogous manner gave a 55% yield of mixed 1- and 2-benzyl-5-benzylmethylaminotetrazole (1:5 based on ^1H nmr analysis), mp 56–57°. The 2 isomer, mp 58–59°, was recovered when the crude product was recrystallized from *n*-hexane.

Anal. Calcd for $C_{16}H_{17}N_5$: C, 68.79; H, 6.14; N, 25.07. Found: C, 68.49; H, 6.09; N, 25.40.

No ylide was found.

5-(3-Chlorobenzyldimethylammonium)tetrazolate.—This ylide, prepared in 33% yield, decomposed at 227–228° after recrystallization from 95% ethanol.

Anal. Calcd for $C_{10}H_{12}N_5Cl$: N, 29.47; Cl, 14.91. Found: N, 29.33; Cl, 15.01.

The ratio of 1- and 2-(3-chlorobenzyl)-5-dimethylaminotetrazoles, also recovered (56% yield) in this alkylation, was 1:10.

Registry No.—2-Benzyl-5-benzylmethylaminotetrazole, 24302-07-6.

The Chemistry of Cumulated Double-Bond Compound. VIII. The Reaction of Phosphonium Ylide with Carbodiimide

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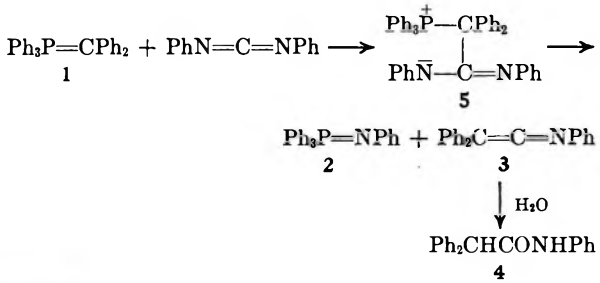
Reactions of phosphonium ylides with ketenes or isocyanates have been reported in a few papers. Luscher had reported that the reaction of diphenylmethylenetriphenylphosphorane with diphenylketene yielded tetraphenylallene and triphenylphosphine oxide.[1] On the other hand, Staudinger and Meyer reported that the reaction of the same ylide with phenyl isocyanate yielded ketenimine.[2] Trippet and Walker observed that the products varied with the structure of ylides.[3]

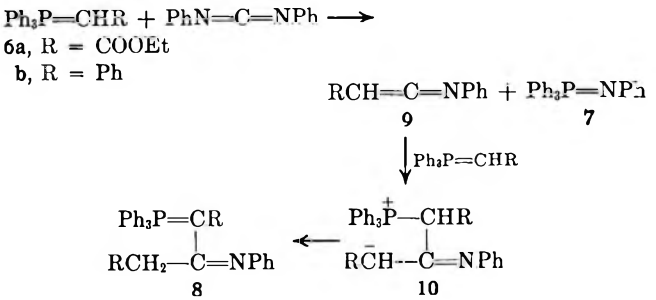
In this paper, we studied the reactions of phosphonium ylides with carbodiimides.

The reaction of diphenylmethylenetriphenylphosphorane (**1**) with diphenylcarbodiimide yielded N-phenyliminotriphenylphosphorane (**2**) and triphenylketenimine (**3**) in good yield. The ketenimine **3** exhibited the principal infrared peak at 2000 cm^{-1} (C=C=N) and was hydrolyzed easily to diphenylacetanilide (**4**). The reaction process seemed to involve



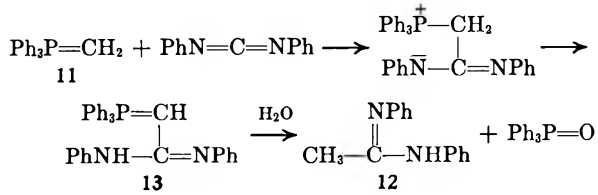
the intermediate **5** according to Wittig-type reaction. Bestmann and Seng[4] reported a similar reaction between phenylmethylenetriphenylphosphorane and benzalaniline to afford stilbene and N-phenyliminotriphenylphosphorane.

In the reaction of the ylides **6**, containing a hydrogen atom on the ylide carbon, diphenylcarbodiimide reacted with two molecules of the ylide **6**, and N-phenyliminotriphenylphosphorane (**7**) and the ylides **8** were obtained.



In the nmr spectrum of the ylide **8a**, the chemical shifts of the two ethyl protons were separated at δ 0.58 (t, CH_3)–3.85 (q, CH_2) and δ 1.02 (t, CH_3)–4.12 (q, CH_2); the methylene group adjacent to the imino group was seen as a singlet at δ 4.11. The infrared spectrum of the ylide **8a** in a Nujol mull indicated the peak at 1570 cm^{-1} (imino group). Similar absorption was observed at 1530 cm^{-1} for the ylide **8b**. In these reactions, the ketenimines **9**, formed in the initial step, react immediately with additional ylide **6** to give **8** *via* the betaine **10** by a prototropic shift.

Methylenetriphenylphosphorane (**11**) reacted with an equimolar quantity of diphenylcarbodiimide in dimethyl sulfoxide; N,N′-diphenylacetamidine (**12**) and triphenylphosphine oxide were obtained by treatment with water. The ylide **13** was not isolated; only the acetamidine **12**, presumably formed by hydrolysis of the ylide **13**, was obtained as a major product.



No reaction was observed between dicylohexylcarbodiimide and the ylides **2** and **6**. This may be due to the lower reactivity of the carbodiimide.

Experimental Section

Preparation of the Carbodiimides.—A mixture of 15.7 g of phenyl isocyanate and 1.73 g of triphenylphosphine was refluxed for 10 hr and distilled to give 8.9 g (70%) of diphenylcarbodiimide, bp 122–127° (1 mm). The physical constants and the infrared spectrum were identical with the reported data.[5]

Dicyclohexylcarbodiimide was purchased and distilled, bp 135–138° (1 mm).

(1) G. Luscher, *Diss. Eidg. Techn. Hochschule, Zurich* (1922); A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 132.
(2) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
(3) S. Trippet and D. M. Walker, *J. Chem. Soc.*, 3874 (1959).
(4) H. J. Bestmann and F. Seng, *Angew. Chem.*, **75**, 475 (1963); *Tetrahedron*, **21**, 1373 (1965).
(5) F. Kurzer and K. Douraghizadeh, *Chem. Rev.*, **67**, 107 (1962).

Preparation of Diphenylmethylenetriphenylphosphorane (1).—The ylide 1 was prepared according to the procedure of Staudinger.[1] The physical properties were identical with reported data.

Preparation of Carbethoxymethylenetriphenylphosphorane (6a).—The ylide **6a** was prepared according to the procedure of Denney and Ross.[6] The physical properties were identical with reported data.

Reaction of Diphenylmethylenetriphenylphosphorane (1) with Diphenylcarbodiimide.—A mixture of 0.025 mol of the ylide **1** and 0.025 mol of diphenylcarbodiimide was stirred at 160–180° for 4 hr under nitrogen stream. The reaction mixture was extracted (petroleum ether), and 4.7 g (53%) of the insoluble solid was separated and recrystallized (ethyl ether) to give N-phenyliminotriphenylphosphorane (2), mp 135–136°.

Anal. Calcd for $C_{24}H_{20}NP$: C, 81.57; H, 5.70; N, 3.96; P, 8.76. Found: C, 81.82; H, 5.64; N, 4.07; P, 8.63.

The extract (petroleum ether) was evaporated to give the yellow solid, ir 2000 cm^{-1}, but recrystallization did not give a pure sample. The column chromatography (Al_2O_3, benzene) of the solid gave 6.8 g (94%) of diphenylacetanilide (4) and 0.2 g of diphenylurea. The acetanilide **4** was identified by ir comparison with an authentic sample and by the mixture melting point test (mmp 185–186°).

Reaction of Carbethoxymethylenetriphenylphosphorane (6a) with Diphenylcarbodiimide.—A mixture of 0.05 mol of the ylide **6a** and 0.025 mol of diphenylcarbodiimide was stirred at 140–150° for 4 hr under nitrogen stream. The reaction mixture was chromatographed (Al_2O_3, benzene) to give 8.2 g (93%) of N-phenyliminotriphenylphosphorane (**7**) and 13.5 g (100%) of the ylide **8a**. The ir spectrum of the iminophosphorane **7** was identical with that of the sample 2 described above. The ylide **8a** was recrystallized (MeOH) to give white crystals: mp 164.5–165.5°; ir (Nujol mull) 1720 (C=O), 1640 (C=O, conjugated to P=C), 1575 cm^{-1} (C=N); nmr (benzene) δ 0.58 (t, 3, J = 7.1 Hz, CH_3), 1.02 (t, 3, J = 7.1 Hz, CH_3), 3.85 (q, 2, CH_2Me), 4.11 (s, 2, $CH_2C{=}N$), 4.12 (q, 2, CH_2Me).

Anal. Calcd for $C_{33}H_{32}O_4NP$: C, 73.72; H, 6.00; N, 2.61; P, 5.76. Found: C, 73.33; H, 5.97; N, 2.69; P, 5.91.

Reaction of Phenylmethylenetriphenylphosphorane (6b) with Diphenylcarbodiimide.—Sodium *t*-butoxide (0.05 mol) and triphenylbenzylphosphonium chloride (0.04 mol) were dissolved in 100 ml of benzene under nitrogen stream. Diphenylcarbodiimide (0.02 mol in 50 ml of benzene) was added dropwise to the solution with stirring over a period of 4 hr at room temperature. Stirring was continued for 3 hr. After separation of 2.1 g (91%) of sodium chloride, the filtrate was concentrated and chromatographed (Al_2O_3, benzene–methanol) to give 0.7 g (10%) of N-phenyliminotriphenylphosphorane, 6.2 g (56%) of triphenylphosphine oxide, 1.4 g (33%) of diphenylurea, and 1.4 g (13%) of the ylide **8b**. Ir spectra of these compounds except the ylide **8b** were identical with those of authentic samples. The ylide **8b** was recrystallized (benzene–hexane) to give yellow crystals: mp 209–210° (lit.[7] 209–210°); mass spectrum (70 eV) m/e 546 (M^+ calcd 546).

Anal. Calcd for $C_{39}H_{32}NP$: C, 85.84; H, 5.91; N, 2.57; P, 5.68. Found: C, 86.11; H, 61.5; N, 2.41; P, 5.51.

Reaction of Methylenetriphenylphosphorane (11) with Diphenylcarbodiimide.—Sodium hydride (0.02 mol) and methylenetriphenylphosphonium bromide (0.02 mol) were dissolved in 140 ml of dimethyl sulfoxide.[8] Diphenylcarbodiimide (0.02 mol) was added dropwise to the solution with stirring; color of the solution changed from yellowish green to deep red. The reaction mixture was allowed to stand for 2 days. The reaction mixture was poured into 200 ml of ice water and extracted with ethyl ether. The ethereal extract was washed (water), dried ($CaSO_4$), concentrated, and chromatographed (Al_2O_3, benzene–methanol) to give 3.3 g (81%) of N,N′-diphenylacetamidine (mp 134–135°) and 5.4 g (97%) of triphenylphosphine oxide. These compounds were identified by ir spectra and mixture melting point test with authentic samples.[9]

Registry No.—2, 2325-27-1; **8a**, 24375-91-5; **8b**, 14630-48-9; diphenylcarbodiimide, 622-16-2.

(6) D. B. Denney and S. T. Ross, *J. Org. Chem.*, **27**, 998 (1962).
(7) R. Huisgen and J. Wulff, *Tetrahedron Lett.*, 917 (1967).
(8) J. Asunskis and H. Schechter, *J. Org. Chem.*, **33**, 1164 (1968).
(9) M. Sen and J. N. Ray, *J. Chem. Soc.*, 646 (1926).

Solvolysis of 9-Bromo-1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane[1]

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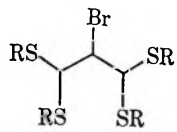
The high solvolytic reactivity of β-halo sulfides has been extensively investigated, particularly that of β-chloroethyl sulfides, the "mustard gases."[2] The effect of sulfur as a neighbouring group[3] is readily demonstrated, for example, by comparing the rates of solvolysis (aqueous dioxane, 100°) of β-chloroethyl ethyl sulfide with that of β-chloroethyl ethyl ether ($k_{sulfide}/k_{ether}$ = 15,000).[4] Halogen atoms in a β relationship to more than one sulfur atom may undergo displacement with still greater facility, and, in accord with this possibility, compounds **1a** and **1b** are described as fuming liquids which lose HBr spontaneously at room temperature.[5]



1a, R = CH_3
b, R = CH_2CH_3

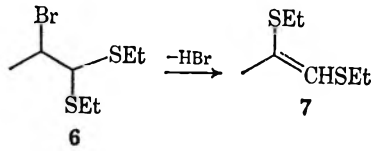
We wish to describe the preparation of a β-halo sulfide which incorporates the functional group arrangement **1** and the results of qualitative solvolysis experiments with this substance (**3**). In the course of an investigation of the chemistry of tetrathiaadamantanes,[6] the reaction of tetramethyltetrathiaadamantane **2** with bromine was examined. With a fourfold excess of bromine, the monobromo derivative **3** was obtained in 33% yield. More highly brominated products may have been formed but could not be isolated.

The structure of the bromide **3** is based mainly on its nmr spectrum. The spectrum contains a six-proton singlet at 1.70 ppm and two three-proton singlets at 1.58 and 1.73 ppm establishing the presence of one pair of equivalent methyl groups and one pair of nonequivalent methyl groups. (For comparison, the CH_3 signals in **2** appear at 1.65 ppm.) The methylene protons appear as a singlet at 2.21 ppm and the proton on the brominated carbon atom appears as a singlet at 4.79 ppm. The substance can be recrystallized from alcohols without serious decomposition. This moderate stability is rather surprising since the *trans*-coplanar stereoelectronic requirement for sulfur-assisted ionization is already satisfied in this rigid system.[7]

(1) Research supported by the National Science Foundation (GP-10950).
(2) Reviewed by E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Chemical Publishing Co., Inc., New York, N. Y., 1960, Vol. II, Chapter 5.
(3) For reviews see K. D. Gunderman, *Angew. Chem. Int. Ed. Engl.*, **2**, 674 (1963); B. Capon, *Quart. Rev.* (London), **18**, 45 (1964); A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 108.
(4) H. Böhme and K. Sell, *Chem. Ber.*, **81**, 123 (1948).
(5) E. Rothstein and R. Whiteley, *J. Chem. Soc.*, 4012 (1953).
(6) D. L. Coffen, P. E. Garrett, and D. R. Williams, *Chem. Comm.*, 652 (1968); K. C. Bank and D. L. Coffen, *ibid.*, 8 (1969).
(7) *Cf.* S. J. Cristol and R. P. Arganbright, *J. Amer. Chem. Soc.*, **79**, 3441 (1957).

When a solution of bromide **3** in glacial acetic acid buffered with sodium acetate is heated under reflux for 2 hr, the bromide is completely transformed into a new substance whose ir spectrum establishes at once that it is not an acetate but an olefin (ν_{max} 1600 cm^{-1}). Structure **5** is assigned to this olefin on the basis of its nmr spectrum. The spectrum contains three three-proton singlets at 1.70, 1.82, and 1.98 ppm indicating three nonequivalent methyl groups. The endocyclic methylene protons appear as an AB quartet at 2.58 ppm (J_{AB} = 14 cps) whence they are no longer equivalent. A one-proton singlet at 4.63 ppm is assigned to the methine proton and two one-proton singlets at 5.12 and 5.31 ppm are assigned to the exocyclic methylene protons. Neither geminal nor allylic coupling is evident for these last three protons.

The rearrangement to tricyclic structure **5** is rationalized in terms of sulfur assisted ionization of the carbon–bromine bond, a 1,2-sulfur shift leading to the cationic intermediate **4**, and subsequent loss of a proton from the adjacent methyl group giving the olefin **5**. Rothstein proposed a similar pathway for the rearrangement of bromide **6** resulting in olefin **7**.[5] It has been suggested, however, that such rearrangements are "best explained by assuming cyclic sulfonium intermediates."[8] Since the 2-adamantyl cation does not undergo a similar rearrangement,[9] the sulfur atoms and not the ring system clearly provide the incentive for compound **3** to rearrange.



6 **7**

Methanolysis of bromide **3** (22 hr at reflux) gave olefin **5** and an unstable by-product assumed to arise from the trapping of cation **4** by methanol. The formation of this by-product was evident from tlc but it changed to olefin **5** during attempts at isolation and purification. Similarly, hydrolysis in aqueous dioxane gave, in addition to olefin **5**, an unstable by-product presumed to be an alcohol formed in the reaction of cation **4** with water.

Experimental Section[10]

9-Bromo-1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane (3).—Bromine (11.0 g, 68 mmol)[11] was added dropwide during 1 hr to a boiling solution of 1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane[12] (4.0 g, 15 mmol) in carbon tetrachloride (250 ml). After a total of 3 hr at reflux, the solution was filtered, washed with aqueous sodium bicarbonate, dried, and evaporated. The residue was triturated with a small amount of ether and chilled, and the crystalline product was filtered out and washed with cold ether. The filtrate contains more bromide (tlc) but, on standing, hydrogen bromide was evolved and a tarry precipitate formed. The crude bromide (1.75 g, 33.6%) was recrystallized from chloroform–isopropyl alcohol giving colorless crystals (70% recovery) with mp 182–4° dec; ir (Nujol) 1400, 1175, 1095, 1065, 1030, 945, 775, and 677 cm^{-1}; nmr ($CDCl_3$) 1.58 (3 H, s), 1.70 (6 H, s), 1.73 (3 H, s), 2.21 (2 H, s), and 4.79 ppm (1 H, s); mass spectrum *m/e* 344 and 342 (M^+ peaks), 263 (ion **4**), 139, 131 (100%), and 59.[13]

Anal. Calcd for $C_{10}H_{16}BrS_4$: C, 34.98; H, 4.40; Br, 23.27; S, 37.35. Found: C, 35.18; H, 4.52; Br, 23.09; S, 37.17.

Acetolysis of Bromide 3.—A solution of bromide **3** (50 mg) and sodium acetate (50 mg) in acetic acid (10 ml) was heated under reflux for 2.5 hr. The acetic acid was evaporated from the cooled solution and the residue was partitioned between methylene chloride and aqueous sodium carbonate. The dried methylene chloride layer left 38 mg (100%) of colorless oil after evaporation which, by tlc, contained only one substance. Crystallization from methanol gave colorless crystals with mp 59–61°; ir (Nujol) 1600, 1170, 1140, 1095, 934, 884, and 740 cm^{-1}; nmr ($CDCl_3$) 1.70 (3 H, s), 1.82 (3 H, s), 1.98 (3 H, s), 2.58 (2 H, AB, J = 14 cps), 4.63 (1 H, s), 5.12 (1 H, s), and 5.31 (1 H, s); mass spectrum *m/e* 262 (M^+), 131, and 59 (100%).

Anal. Calcd for $C_{10}H_{14}S_4$: C, 45.76; H, 5.38; S, 48.86. Found: C, 45.83; H, 5.52; S, 48.89.

Registry No.—**3**, 24378-10-7; **5**, 24378-11-8.

(8) W. E. Parham, J. Heberling, and H. Wynberg, *J. Amer. Chem. Soc.*, **77**, 1169 (1955).

(9) P. von R. Schleyer and R. D. Nicholas, *ibid.*, **83**, 182 (1961).

(10) Melting points are uncorrected. Ir, nmr, and mass spectra were recorded on Perkin-Elmer 137, Varian A-60A, and Atlas CH-7 instruments respectively. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

(11) With less bromine the product contains starting material.

(12) K. Olsson and S-O Almquist, *Ark. Kemi*, **27**, 571 (1967).

(13) The electron-impact fragmentation reactions of tetrathiaadamantanes are discussed by K. Olsson, *ibid.*, **26**, 435 (1967), and K. Olsson and S-O Almquist, ref 12.

The Alkylation of Amine Sulfides[1]

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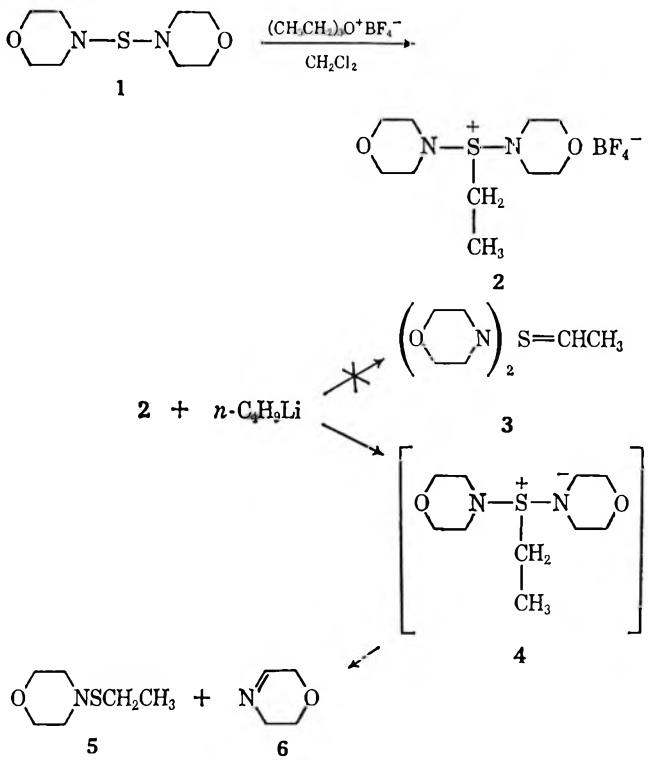
Received December 4, 1969

It has been shown that trialkyloxonium salts alkylate several types of organic sulfur compounds,[2] and that treatment of dithiocarbamates with trialkyloxonium salts or with less reactive alkylating agents yields the S-alkylated symmetrical products[3] instead of other possible unsymmetrical structures.

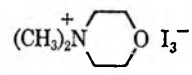
This note demonstrates a successful alkylation of an amine sulfide **1** by triethyloxonium fluoroborate to give the novel resonance-stabilized sulfonium salt **2**. Numerous other alkylation reactions on amine sulfides with a variety of alkylating agents did not lead to isolatable products analogous to **2**.



The structure of **2** (obtained in 30–40% yield) was assigned on the basis of the elementary analysis and the very characteristic nmr spectrum; the latter showed the characteristic sharp complex triplets of the methylene protons of the morpholine rings, which were shown by morpholine sulfide itself. The methylene triplets at 3.80 and 3.52 ppm were present in a 1:1 ratio, as in morpholine sulfide. This rules out structures for the alkylation product in which the ethyl group is on nitrogen or oxygen of the morpholine rings, because such onium compounds would show a shift to lower field of two pairs of methylene protons, and the symmetrical arrangement of the methylene protons in morpholine sulfide would disappear. Furthermore, the nmr spectrum of **2** showed a sharp triplet at 1.39 ppm, due to the CH_3 protons of the ethyl group; portions of the expected quartet for the CH_2 protons of the ethyl attached to sulfur were distinguishable at the base of the morpholine proton absorption. The integration of the nmr spectrum agreed completely with structure **2**.

Treatment of the sulfonium salt **2** with *n*-butyllithium, with later addition of benzophenone, yielded 37% of the sulfenamide **5** (which was identified by synthesis), with 90% recovery of the benzophenone. The sulfenamide was probably formed by abstraction of an α proton from the morpholino methylene group, to give **4** which then formed the sulfenamide **5** and the morpholine derivative **6** or products derived from **6**. No evidence was obtained for the formation of the ylide **3**.

Of the many other alkylation processes tried on several amine sulfides, treatment of **1** with methyl iodide was the only one giving an identifiable product; a violet solid, N,N-dimethylmorpholinium triiodide **7** was obtained, as well as a small amount of N,N-dimethylmorpholinium iodide. The formation of the triiodide may be explained by a scheme analogous to that worked out by Heimer and Field[4] for the action of methyl iodide on sulfenamides.



7

Experimental Section[5]

Alkylation of Morpholine Sulfide with Triethyloxonium Fluoroborate to Yield 2.—Morpholine sulfide[6] (2.37 g) and triethyloxonium fluoroborate[7] (2.20 g) were refluxed for 1.5 hr in methylene chloride. The dark red solution was cooled, 25 ml of anhydrous ether was added dropwise with stirring, and the ether was decanted from the red oil which separated. After two similar treatments with 10 ml of ether, the partially solidified oil was dissolved in 15 ml of hot methanol, and the solution was cooled in a refrigerator. The resulting tan ethyldimorpholinosulfonium fluoroborate (**2**) was collected and washed with 5 ml of cold methanol; it melted at 171.5–172.5° (dec) and weighed 1.22 g (32%). The nmr spectrum, taken in D_2O with 1% of DDS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) has been discussed above. An analytical sample of **2**, mp 181–182°, was prepared by repeated recrystallizations from anhydrous methanol followed by drying at 56° (0.5 mm).

Anal. Calcd for $C_{10}H_{21}BF_4N_2O_2S$: C, 37.51; H, 6.61; S, 10.02. Found: C, 36.99; 38.20; H, 6.79, 6.56; S, 10.28.

In other runs, the methylene chloride solution and the ether washes from **2** were shown to contain a mixture of morpholine sulfide **1** and the corresponding disulfide, by nmr studies, by elemental sulfur analysis, and by isolation of crystalline disulfide in one case, mp 122–124°; the reported[6] value is 124–125°.

The OCH_2 protons of the disulfide and monosulfide were coincident from 3.50 to 3.80. The NCH_2 protons of the sulfide were from 3.13 to 3.38 with the same protons in the disulfide from 2.70 to 2.95. These values were shown by the mixture and also by authentic samples taken separately.

Formation of the Sulfenamide 5 by Butyllithium and the Sulfonium Salt 2.—A slurry of 1.00 g (0.0031 mol) of **2** in 100 ml of tetrahydrofuran (predistilled from lithium aluminum

(1) Aided by Grant 2252-C from the Petroleum Research Fund of the American Chemical Society.

(2) Cf. G. K. Helmkamp, H. N. Cassey, B. A. Olsen, and D. J. Pettitt, *J. Org. Chem.*, **30**, 933 (1965). D. J. Pettitt and G. K. Helmkamp, *ibid.*, **28**, 2932 (1963); **29**, 2702 (1964).

(3) J. L. Richards, D. S. Tarbell, and E. H. Hoffmeister, *Tetrahedron*, **24**, 6485 (1968).

(4) N. Heimer and L. Field, *J. Org. Chem.*, in press.

(5) Microanalyses were by Galbraith Laboratories; ir spectra were taken on a Beckman IR-10 spectrometer and nmr spectra on a Varian A-60. TMS was used as an internal standard unless otherwise specified, and chemical shifts are reported in parts per million.

(6) E. S. Blake, *J. Amer. Chem. Soc.*, **65**, 1267 (1943).

(7) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

hydride) in a nitrogen atmosphere was stirred in an ice bath. To this, a solution of 1.4 ml of a 22% *n*-butyllithium–hexane mixture (0.0031 mol of *n*-butyllithium) in 15 ml of tetrahydrofuran was added dropwise. The colorless slurry turned yellow and, after 0.15 hr, the reaction was warmed and heated at reflux for 0.15 hr. The reaction was cooled, a solution of 0.547 g (0.003 mol) of benzophenone in 15 ml of tetrahydrofuran was added dropwise, and, after the mixture stirred for 1 hr at room temperature, 700 ml of water was added, which precipitated a solid. Extraction with two portions of ether yielded 0.96 g of a mixture of a liquid and an oily solid. The nmr spectrum in chloroform indicated that the mixture consisted of benzophenone and morpholine or derivative thereof.

A short-path vacuum distillation of 0.70 g of the mixture gave 0.48 g of distillate (the distillation was not continued to dryness), collected at 0.50 mm (pot temperature 100–140°). Tlc of the distillate showed only one spot—a streak, R_f 0.55–0.75. A sample of reactant benzophenone showed a similar R_f value and the ir spectrum of the distillate (liquid film) showed a strong band at 1660 cm^{-1}, which is characteristic of benzophenone.[8] The nmr spectrum of the distillate showed a triplet at 1.22, a quartet at 2.73 and overlapping into the NCH_2 absorption of morpholine centered at 2.95, the OCH_2 absorption at 3.65, and aromatic protons from 7.24 to 7.92. The integration was 19 (triplet): 36 (total of quartet and NCH_2):24:158. These data suggested that the distillate was a mixture of benzophenone and either N-ethylmorpholine or the sulfenamide **5** [N-(ethylthio)morpholine].

Vpc of the distillate (10 ft × 1/4 in. 10% SE-30 on 80–100S, column temperature 180°, flow rate 24 ml of He/min) showed seven peaks, with those at 4.3 and 27 min accounting for 95% of the material. The 4.3-min peak corresponded with the retention time of an authentic sample of the sulfenamide **5** (prepared as below), and coinjection enhanced this peak without showing additional peaks. Furthermore, the chemical shifts observed for the ethyl and morpholine protons in the mixture were identical with those for the sulfenamide **5**. The broad peak at 27 min was identical in shape and retention time with that obtained from injection of an acetone solution of benzophenone. An injection of the benzophenone solution and the mixture increased the 27-min peak with the only additional peak observed due to acetone at 1 min.

Based on the nmr integrations, the minimum yields were 36% sulfenamide and 90% recovery of benzophenone.

N-(Ethylthio)morpholine. The Sulfenamide 5.—Chlorine (0.5 ml, 0.11 mol, trapped in a Dry Ice–acetone bath) was allowed to evaporate and the vapors were passed over a stirred solution of 12.3 ml (0.1 mol) of ethyl disulfide (Aldrich) in 50 ml of petroleum ether at −20°. The reaction was stirred for an additional 0.25 hr after complete evaporation of the chlorine. The yellow solution was added in portions to a stirred solution of 53 ml (0.6 mol) of morpholine in 200 ml of petroleum ether in an ice bath. The white slurry that resulted was extracted with three portions of water to remove morpholine hydrochloride. The petroleum ether solution was dried and concentrated. Distillation of the residue gave 20.75 g (72%) of colorless sulfenamide, bp 76–77° (14 mm). Its nmr spectrum showed a triplet at 1.22 (3 H) and a quartet centered at 2.72 (SCH_2) which overlapped into a complex triplet at 2.93 for the NCH_2 (total of 6 H) and with the OCH_2 at 3.62 integrating for 4 H.

Anal. Calcd for $C_6H_{13}NOS$: C, 48.94; H, 8.90. Found: C, 48.69; H, 8.63.

N,N-Dimethylmorpholinium Triiodide (7) from Sulfide and Methyl Iodide.—A solution of 2.50 g (0.012 mol) of morpholine sulfide and excess methyl iodide (7.5 ml, 0.12 mol) in 15 ml of methylene chloride was stirred for 16 hr at room temperature. The resulting solid was collected and washed with 15 ml of cold methylene chloride; the product was 2.00 g of dark violet solid, mp 118–122° dec. The nmr spectrum of the crude product (in acetonitrile) showed only the absorptions expected for N,N-dimethylmorpholinium iodide. Recrystallization of the product from 25 ml of methanol gave 0.841 g of violet solid, mp 118–119°. Repeated recrystallizations from methanol gave a violet solid, mp 125–126° (apparently with decomposition). Although the solid had the same melting point as morpholine sulfide, its color, the depression of a mixture melting point, and its nmr spectrum showed it to be a different compound. The nmr spectrum (in acetonitrile, TMS as reference) showed the characteristic complex triplets of the morpholine ring from 3.70 to 4.10 (OCH_2) and 3.22 to 3.57 (NCH_2) with a singlet at 3.18. The integration was 4:4:6 respectively. The elemental analysis was correct for N,N-dimethylmorpholinium triiodide.

Anal. Calcd for $C_6H_{14}I_3NO$: C, 14.50; H, 2.84; I, 76.62; N, 2.82. Found: C, 14.52; H, 2.86; I, 76.60; N, 2.83.

Evaporation of the red filtrate from the first recrystallization gave 0.65 g of pale violet solid, mp 188–205°, which, after crystallization from 2 ml of hot methanol, yielded a small amount of the violet triiodide. Further concentration of the filtrate gave a small amount of white crystals, mp 245.5–247° dec; the melting point and nmr spectrum of the crude solid indicated that it was N,N-dimethylmorpholinium iodide, reported[9] to melt at 246°.

Registry No.—**2**, 24407-43-0; **5**, 24378-12-9; **7**, 24378-13-0.

(8) H. W. Thompson and P. Torkington, *J. Chem. Soc.*, 640 (1945).

(9) L. Knorr, *Ann.*, **301**, 1 (1898).

Triphasiaxanthin, a New Carotenone[1]

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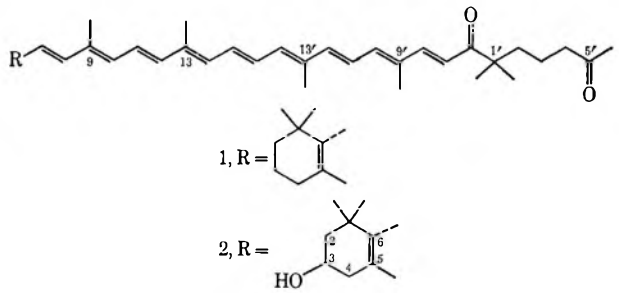
Semi-β-carotenone (**1**) occurs as the principal carotenoid constituent in the fruit of the *Citrus* relative



Triphasia trifolia.[3] A new, more polar carotenone, triphasiaxanthin, was isolated.

The visible absorption spectrum of triphasiaxanthin was very similar to that of the semi-β-carotenone. Its infrared spectrum indicated the presence of two carbonyl groups: saturated, 1715 cm^{-1}; and conjugated, 1660 cm^{-1}. Reduction with $LiAlH_4$ caused a hypsochromic shift (*ca.* 25 nm) in the visible absorption maxima. Taken together these evidences indicated a decaenone chromophore in the isolated pigment.

The infrared spectrum also indicated the presence of a secondary hydroxyl group (3450 and 1025 cm^{-1}). Tlc[4] tests indicated the facile quantitative formation of the trimethylsilyl derivative on silylation of the new carotenone. On allylic oxidation with nickel peroxide[5] or on treatment with acid chloroform, no bathochromic shift in the visible absorption maxima

(1) Part X in the series Citrus Carotenoids.

(2) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(3) H. Yokoyama and M. J. White, *Phytochemistry*, **7**, 1031 (1968).

(4) A. McCormick and S. L. Jensen, *Acta Chem. Scand.*, **20**, 1989 (1966).

(5) K. Nakagawa, R. Konaka, and T. Nakata, *J. Org. Chem.*, **27**, 1597 (1962).

TABLE I
CHARACTERISTIC FRAGMENTS FROM HIGH RESOLUTION MASS SPECTRUM OF TRIPHASIAXANTHIN

Intensity	m/e Measured	m/e Calcd	Formula	Remarks
15.78	584.4221	584.4215	$C_{40}H_{56}O_3$	Mol-ion (molecular ion)
4.48	582.4066	582.4059	$C_{40}H_{54}O_3$	Mol-ion − H_2
5.10	566.4150	566.4110	$C_{40}H_{54}O_2$	Mol-ion − H_2O
5.47	564.4017	564.3967	$C_{40}H_{52}O_2$	$(M^+ - H_2) - H_2O$
1.42	492.3586	492.3591	$C_{33}H_{48}O_3$	Mol-ion − C_7H_8 (toluene)
16.53	478.3396	478.3435	$C_{32}H_{46}O_3$	Mol-ion − C_8H_{10} (xylene)
1.05	474.3481	474.3486	$C_{33}H_{46}O_2$	Mol-ion − $C_7H_{10}O$ (toluene + water)
4.04	470.3210	470.3174	$C_{33}H_{42}O_2$	Mol-ion − $C_7H_{14}O$ (loss of terminal carbonyl and rearrangement)
1.45	460.3337	460.3330	$C_{32}H_{44}O_2$	Mol-ion − $C_8H_{12}O$ (xylene + water)
0.55	445.3084	445.3096	$C_{31}H_{42}O_2$	Mol-ion − cleavage at C-6 with loss of OH
1.32	428.3045	428.3069	$C_{31}H_{40}O_1$	Mol-ion − cleavage at C-6 with loss of two carbonyl groups

of triphasiaxanthin was observed, indicating that the hydroxy group is not in the allylic position.

The nmr spectrum of triphasiaxanthin contained ten C-methyl resonances. In addition to a methyl ketone methyl at τ 7.89 (C-5′, 3 H), the nmr spectrum revealed four in-chain olefinic methyls at τ 8.00 (C-9, C-13, C-9′, and C-13′, 12 H) and two geminal methyls at τ 8.82 (C-1′, 6 H). These values are to be compared with similar values (τ 7.89, 8.00, and 8.82) recorded for semi-β-carotenone.[3] The nmr properties of triphasiaxanthin indicated the presence of the β-cyclogeranylidene ring end group. As in the β-ring end group of reticulataxanthin,[6] two geminal methyl groups are equivalent at τ 8.92 (C-1, 6 H), and a single methyl is at τ 8.26 (C-5, 3 H). The hydroxy group appears to be located at C-3 in the β-ring end group. This is indicated by the close agreement in values of the C-methyl resonances of the three methyl groups in the β rings of triphasiaxanthin and reticulaxanthin. The two geminal methyl groups at C-1 are equivalent at τ 8.92, as is common for 3-hydroxy β rings, but might not be equivalent with the hydroxy group in the 2 or 4 (allylic) position. Moreover, with the hydroxy group in the 4 position, the signal of the C-5 methyl group would be expected to be downfield from the observed value.[7]

On the basis of evidence cited above, triphasiaxanthin has been assigned structure **2**.

The mass spectrum (Table I) of triphasiaxanthin ($C_{40}H_{56}O_3$ = 584.4215) is in good accord with structure **2**. The presence of a single hydroxyl group in the ring is indicated by the loss of only one molecule of water and the loss of the ring ($C_9H_{15}O$). The loss of $C_9H_{16}O_2$ is in good agreement with the proposed structure at the acyclic end of the molecule. As expected,[8] the characteristic ions representing the loss of C_7H_8 and C_8H_{10} from both the parent and the parent minus water are found.

In addition to the ions belonging to triphasiaxanthin, ions from at least two impurities were discovered in one of the samples. The first of these has a peak of *m/e* 600.4338 corresponding to $C_{44}H_{56}O$ (600.4331). The second impurity has an apparent molecular ion at 568.4334 corresponding to $C_{40}H_{56}O_2$ (568.4280) and a parent less water at 550.4129 ($C_{40}H_{54}O$ = 550.4161). The identity of these two substances is under investigation and will be reported later.

(6) H. Yokoyama, M. J. White, and C. E. Vandercook, *J. Org. Chem.*, **30**, 2482 (1965).
(7) B. C. L. Weedon, "Chemistry and Biochemistry of Plant Pigments," T. W. Goodwin, Ed., Academic Press Inc., New York, N. Y., p 94.
(8) U. Schwieter, H. R. Bolliger, L. H. Chopard-Dit-Jean, G. Englert, M. Kofler, A. Planta, R. Ruegg, W. Vetter, and O. Isler, *Chimia*, **19**, 294 (1965).

Experimental Section

Nmr data were obtained at 100 MHz and refer to deuteriochloroform solutions; the chemical shifts are in τ values relative to internal tetramethylsilane. The high resolution mass spectra were obtained on an AEI Type MS 902 mass spectrometer. All peaks were measured with an average error of less than 5 ppm at a resolving power of 1/10,000. No data with an error >10 ppm were accepted. Samples were introduced by means of a heatable probe[9] at temperatures ranging from 159 to 200°. PFK was used as a reference compound for mass measurement. The fruit collection was made in Feb 1968, by Mr. N. Almeyda at the Federal Experiment Station of the U. S. Department of Agriculture, Mayaguez, Puerto Rico.

Isolation of Triphasiaxanthin.—The carotenoid pigments were extracted from the fruits (400 g) in the manner described previously.[3] The carotenoid mixture was phase-partitioned between petroleum ether–98% methanol. The hypophase was submitted to column chromatography on Microcel C, using 15% acetone in a petroleum ether solvent system. The isolated pigment was crystallized from peroxide-free ether–petroleum ether, yielding 8 mg: mp 95–97° (evacuated capillary, uncorrected); λ_{max} ($CHCl_3$) 480 nm ($\epsilon \times 10^{-3}$ 96.6), 510 (84.9); λ_{max} (*n*-hexane) 440, 467, 495 nm; ir ν (KBr pellet) 3450, 1715, 1660, 1025 cm^{-1}; nmr signals[10] at 7.89 (s, 3 H), 8.00 (s, 12 H), 8.26 (s, 3 H), 8.82 (s, 6 H), and 8.92 (s, 6 H).

Reduction of Triphasiaxanthin.—Reduction of triphasiaxanthin (0.5 mg) with $LiAlH_4$ in dry ether afforded the reduced product: λ_{max} (*n*-hexane), 420, 442, 471 nm.

TMS Derivative of Triphasiaxanthin.—Treatment of the isolated pigment (0.5 mg) in dry pyridine (1 ml) with hexamethyldisilazane (0.5 ml) and trimethylchlorosilane (0.3 ml) for 30 min resulted in the quantitative formation of triphasiaxanthin trimethyl silylether as judged by tlc.

Attempted Oxidation of Triphasiaxanthin.—Triphasiaxanthin (2 mg) in 5 ml benzene was treated with NiO_2 (30 mg, available oxygen 4.1×10^{-3} g-atom/g of NiO_2 determined by titration) for 60 min.[4] No bathochromic shift in its visible absorption maxima was observed.

Attempted Dehydration of Triphasiaxanthin.—Triphasiaxanthin (1 mg) in 5 ml of $CHCl_3$ was treated with 4 drops of chloroform–HCl reagent and allowed to stand at room temperature for 10 min. The mixture was then washed with sodium bicarbonate solution and water and dried over anhydrous Na_2SO_4. The visible spectrum remained unchanged.

Registry No.—2, 23939-69-7.

(9) H. G. Boettger and A. M. Kelly, 17th Annual Conference on Mass Spectrometry and Allied Topics, Dallas, Texas, May 1969.
(10) C-Methyls only.

Acknowledgments.—The authors are indebted to Dr. Robert Lundin for the nmr spectra and to Dr. H. M. Gaskins, Officer-in-Charge, and Mr. N. Almeyda of the Federal Experiment Station for the fruit collections.

An Efficient Synthesis of Symmetrical 1,3-Diglycerides[1]

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The symmetrical 1,3-diglycerides have been obtained by a variety of procedures, most of which involve protecting groups requiring chemical or catalytic cleavage.[3] Syntheses of the unsymmetrical 1,2-diglycerides also require the use of protective groupings which must be removed under very mild conditions in order to prevent acyl migration from the C-2 to the terminal positions. Hydrogenolysis overcomes this problem but limits the route to the synthesis of saturated diglycerides.

Recently, Windholz and coworkers[4] described the use of β,β,β-trichloroethoxycarbonyl chloride as a generally applicable protecting group for hydroxyl and amino functions. The carbonates and urethans formed are stable under a variety of oxidation and reduction conditions but are easily removed by treatment with zinc dust in acetic acid or methanol.

This reagent has been utilized by Pfeiffer[5] in the synthesis of 1,2-diglycerides thus avoiding many of the drawbacks of the earlier methods. There is as yet, however, no satisfactory synthetic approach to the synthesis of the symmetrical 1,3-diglycerides, particularly those with unsaturated side chains.

Rearrangement of the 1-iodo-2,3-diglyceride by refluxing with silver nitrite in 80% aqueous alcohol,[6] a convenient procedure for the synthesis of saturated 1,3-diglycerides, proved unsatisfactory in our hands for the corresponding unsaturated compounds owing to silver catalyzed isomerization of the olefinic center. The catalytic part played by the silver in this rearrangement was established by treating pure oleic acid with silver nitrite under the prescribed experimental conditions, *viz.*, reflux in 80% aqueous alcohol for 2–3 hr—this produced a mixture containing 32% elaidic acid.

Use of dihydroxyacetone as a starting material has been examined by Barry and Craig,[7] but the synthetic sequence used was elaborate, requiring the protection of the carbonyl group as a mercaptal, and no further work has appeared in the literature since that time. We have found that dihydroxyacetone is an ideal starting material for the synthesis of long-chain 1,3-diglycerides, *i.e.*, glycerol 1,3-dipalmitate and -dioleate since it is readily acylated with a fatty acid chloride in the presence of pyridine in high yield and the central keto group rapidly reduced by borohydride in tetrahydrofuran solution at 5° to give the 1,3-diglyceride without detectable amounts, by thin layer chromatography, of the 1,2-diglycerides. Synthesis of short-chain diglycerides is also possible by this method, but results are less satisfactory. In a typical experiment glycerol 1,3-diacetate was obtained in over 80% yield but when examined by nmr was shown to contain approximately 10% 1,2 isomer.

Experimental Section[8]

1,3-Dihydroxypropan-2-one 1,3-Diacetate.—Dihydroxy acetone (15.0 g) was dissolved in pyridine (50 ml) and acetic anhydride (50 ml). After 1 hr at 20°, the solvents were removed as completely as possible by vacuum distillation. The residue, dissolved in ethyl acetate, was washed with water, 3% aqueous hydrochloric acid, and water and dried. Evaporation and crystallization from benzene–hexane gave the diacetate (22.9 g, 81%) as long colorless needles, mp 46–47° (lit.[9] mp 46–47°).

1,2,3-Trihydroxypropane 1,3-Diacetate.—The above diacetate (10.0 g) was dissolved in tetrahydrofuran (150 ml), and water (10 ml) and treated portionwise at 5° with neutral sodium borohydride (2 g).[10] After 30 min excess borohydride was destroyed by dropwise additon of glacial acetic acid (1 ml), and the solution was diluted with chloroform, washed with water, aqueous sodium bicarbonate, and water, and dried over magnesium sulfate. Evaporation gave the diacetate as a colorless oil (9.10 g), bp 150° (12 mm) [lit.[11] bp 149° (12 mm)]. The nmr, however, showed a peak at δ 3.75 ($CDCl_3$ solution, unesterified $-CH_2OH$) indicating the presence of up to 10% 1,2 isomer.

1,3-Dihydroxypropan-2-one 1,3-Dioleate.—Dihydroxyacetone (3.0 g) was stirred under nitrogen in chloroform (150 ml). To this heterogeneous mixture was added oleoyl chloride (20 ml) in chloroform (150 ml) followed by anhydrous pyridine (10 ml). After 30-min stirring at room temperature the reaction mixture became homogeneous and 1 hr later no trace of acid chloride could be detected. The bulk of the solvent was removed under vacuum. The residue was shaken with water and ethyl acetate and the organic layer separated. The aqueous layer was again shaken with ethyl acetate and the combined extracts were washed with water, dried over sodium sulfate, and evaporated. The resulting final oil was recrystallized from methanol to give 1,3-dihydroxypropan-2-one 1,3-dioleate (15.8 g, 76%) as small plates, mp 43–44°.

Anal. Calcd for $C_{39}H_{70}O_5$: C, 75.80; H, 11.4. Found: C, 75.85; H, 11.04.

1,2,3-Trihydroxypropane 1,3-Dioleate.—The dioleate (10 g) was dissolved in tetrahydrofuran (150 ml) and water (10 ml). The heterogeneous solution was chilled to 5° and sodium borohydride[10] (1.0 g) added in small portions. After reaction and work-up as described above, an oil (9.0 g, 89%) was obtained which partially crystallized to give 1,2,3-trihydroxypropane 1,3-dioleate as needles, mp 20–22° (lit.[3] mp 25°). No trace of the 1,2 isomer was detected by thin layer chromatography [tlc system hexane–ethyl acetate (6:1)].

1,3-Dihydroxypropan-2-one 1,3-Dipalmitate.—Dihydroxyacetone (7.0 g) was stirred in chloroform (300 ml) under nitrogen at room temperature. To this was added palymitoyl chloride (44 g) followed by anhydrous pyridine (15 ml). The heterogeneous mixture was stirred for 3 hr and diluted with water and the chloroform layer separated. The aqueous layer was extracted

(1) Contribution No. 371 from the Institute of Organic Chemistry, Syntex Research. For No. 370, see H. Carpio, P. Crabbé, and W. Rooks, *J. Med. Chem.*, in press.

(2) Syntex Postdoctoral Fellow, 1967–1968.

(3) L. Hartman, *Chem. Rev.*, **58**, 845 (1958).

(4) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).

(5) (a) F. R. Pfeiffer *et al.*, *ibid.*, 3549 (1968); (b) F. R. Pfeiffer *et al.*, *J. Org. Chem.*, **34**, 2795 (1969).

(6) F. L. Jackson, Ph.D. Thesis, Pittsburgh University, Pittsburgh, Pa., 1943.

(7) P. J. Barry and B. M. Craig, *Can. J. Chem.*, **33**, 716 (1955).

(8) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Boiling points are uncorrected. Microanalyses were performed in the Microanalytical Laboratory of Dr. A. Bernhardt, Max Planck Institute, West Germany.

(9) "Heilbron's Dictionary of Organic Compounds," Vol. 2, Oxford University Press, Oxford, England, 1965, p 1046.

(10) The sodium borohydride used was first stirred in ethyl acetate overnight, washed with ether, and dried. Thanks are due to Dr. Ian Harrison for suggesting this procedure.

(11) See ref 9, p 845.

with two 50-ml portions of chloroform and the chloroform solutions were combined and washed once with water. Concentration of the chloroform to small volume resulted in the precipitation of a crystalline solid which was recrystallized from methylene chloride–ether to give 1,3-dihydroxypropan-2-one 1,3-dipalmitate (37 g, 84%) as small plates, mp 81–82°.

Anal. Calcd for $C_{35}H_{66}O_5$: C, 74.0; H, 11.7. Found: C, 73.6; H, 11.5.

1,2,3-Trihydroxypropane 1,3-Dipalmitate.—1,3-Dihydroxypropan-2-one 1,3-dipalmitate (10.0 g) was dissolved in a mixture of tetrahydrofuran (250 ml) and benzene (50 ml). Water (15 ml) was slowly added to this solution with stirring and the temperature of the mixture reduced to approximately 5° by external cooling in an ice bath; a milky-white suspension resulted. Sodium borohydride[10] (1.0 g) was added to this heterogeneous mixture; after a further 30 min, the reaction mixture was worked up as described above to give 1,2,3-trihydroxypropane 1,3-dipalmitate (10 g, 99%) as a waxy white solid, mp 67–68°, which was recrystallized from chloroform to give mp 72–73° (lit.[12] mp 72–74°). Thin layer chromatography showed no trace of the 1,2 isomer [tlc system hexane–ethyl acetate (6:1)].

Registry No.—1,3-Dihydroxypropan-2-one 1,3-dioleate, 24472-44-4; 1,3-dihydroxypropan-2-one 1,3-dipalmitate, 24472-45-5.

(12) See ref 9, Vol. 3, p 1267.

Cyclization at the Less Nucleophilic Center of a β-Diketone Dicarbanion through a Dicarbanion–Benzyne Intermediate[1]

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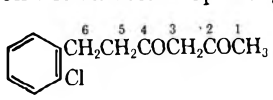
Bunnett and Skorcz[2] have shown that addition of 6-(*o*-chlorophenyl)-2,4-hexanedione (**1**) to excess potassium amide in liquid ammonia affords 1-acetyl-2-tetralone (**2**). A study of the possible intermediates in this cyclization promised to be of particular interest since, although monocarbanion–benzyne **3** appeared to be the intermediate that cyclizes, dicarbanion–benzyne **4** may be the intermediate that cyclizes to give **2**. If so, this would be the first example where the less nucleophilic 3-carbanionic center of a β-diketone dicarbanion reacts preferentially to the much more nucleophilic terminal 1-carbanionic center of such a β-diketone dicarbanion with an electrophilic group.[3]



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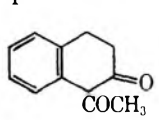

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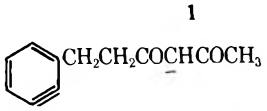

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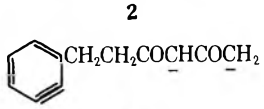
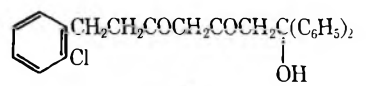
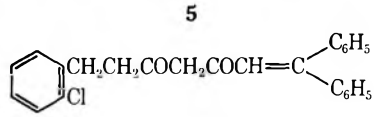


4

We have obtained evidence that dicarbanion–benzyne **4** is indeed the principal intermediate that cyclizes to give **2**, and that the monocarbanion and dicarbanion are formed at a faster rate than an appreciable amount of benzyne, the electrophilic center for cyclization to **2**. Thus, not only could chloro β-diketone **1** be recovered after conversion to its monocarbanion or dicarbanion salts by direct or inverse addition of 1 or 2 mol equiv of potassium amide in liquid ammonia, but the dicarbanion was also condensed at its terminal position with benzophenone to give carbinol-β-diketone **5**. This mode of intermolecular condensation is characteristic of such 1,3 dicarbanions.[3] The yield of **5** was 41%, which is approximately the same as that reported (42%) earlier for cyclic β-diketone **2**.[2]



5



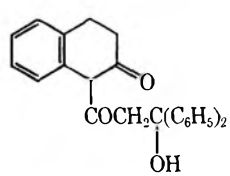
6

The structure of **5** was supported, not only by analysis and absorption spectra, but also by dehydration with acid to give β-diketo olefin **6** in 30% yield. The structure of **6** was also supported by analysis and absorption spectra.

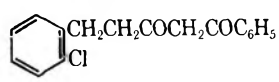
The conversion of chloro β-diketone **1** to its monocarbanion was accompanied by slight coloration which was probably due to a trace amount of benzyne formation. The related β-diketone, 6-phenyl-2,4-hexanedione, which has no chlorine failed to produce coloration under similar conditions. In both cases the β-diketone was recovered quantitatively upon acidification.

The conversion of chloro β-diketone **1** to its dicarbanion was accompanied by distinct coloration, but only **1** was recovered after neutralization; none of **2** was found.

Cyclic β-diketone **2** was converted to its dipotassio salt and condensed with benzophenone to form carbinol-β-diketone **7** in 73% yield; on prolonged standing, **7** underwent dehydration to give the unsaturated β-diketone which was isolated as the pyrazole derivative.



7



8

In contrast to chloro β-diketone **1**, chloro β-diketone **8** failed to afford an isolable product when treated with 2 molar equiv of potassium amide in liquid ammonia followed by 1 molar equiv of benzyl chloride or benzophenone, and, when **8** was treated with excess potassium amide in liquid ammonia, a polymeric material was obtained. The isolation of polymeric material suggests that an intermolecular condensation may have taken precedence over an intramolecular cyclization.

The starting chloro β-diketones **1** and **8** were readily prepared from *o*-chlorobenzyl chloride and the dicarbanions of acetylacetone and benzoylacetone, respectively. Chloro β-diketone **1** can now be made in a

(1) Supported by the National Science Foundation.

(2) J. F. Bunnett and J. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).

(3) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958); R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961); T. M. Harris and C. R. Hauser, *ibid.*, **29**, 1391 (1964).

single step which is more convenient than the three-step method formerly employed.[2]

Experimental Section

Melting points were taken on a Thomas–Hoover melting point apparatus in open tubes and are uncorrected. Analyses were performed by M-H-W Laboratories, Garden City, Mich., and by Janssen Pharmaceutica, Beerse, Belgium. Ir spectra were obtained with a Perkin-Elmer Model 137 or 237 spectrometer. Nmr spectra were obtained on a Varian A-60 nuclear magnetic resonance spectrometer, and shifts are reported in parts per million downfield (δ) from an internal tetramethylsilane (TMS) standard.

Preparation of 6-(*o*-Chlorophenyl)-2,4-hexanedione (1).—To a stirred slurry of 0.828 mol of $NaNH_2$[4] in 500 ml of anhydrous NH_3(l), cooled with a Dry Ice–acetone bath and blanketed with nitrogen, was added 43.5 g (0.435 mol) of acetylacetone in 50 ml of dry ether. The resulting mixture was stirred for 20 min, followed by the addition, during 7 min, of 58.2 g (0.362 mol) of *o*-chlorobenzyl chloride in 50 ml of dry ether. At the end of a 2-hr stirring period, the ammonia was evaporated as 250 ml of dry ether was added. Crushed ice (100 g) was then added, followed by 70 ml of concentrated HCl. The layers were separated, and the aqueous layer was extracted with three 100-ml portions of ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was distilled to give 59.2 g (73%) of 6-(*o*-chlorophenyl)-2,4-hexanedione (1): bp 143° (3 mm) [lit.[2] bp 120–123° (2 mm)]; ir (neat) 3096, 1667, 1610, 1449, 1318, 1279, 947, 925, 814, and 766 cm^{-1}; nmr (CCl_4) δ 1.90 (s, 3 H, CH_3–), 2.0–3.15 (m, 4 H, $-CH_2CH_2-$), 5.30 (s, 1 H, C_3 H_{enol}), and 6.75–7.3 (m, 4 H, Ar–H).

The melting point of the pyrazole of 1 prepared in the standard manner was 66–68° (ligroin) [(lit.[2] mp 67–68°)]. Compound 1 also gave a violet ferric chloride test.

Cyclization of 1 to Form 1-Acetyl-2-tetralone (2).—A solution of 0.263 mol of potassium amide in NH_3(l) was added, during 20 min, to a well-stirred solution of 11.23 g (0.05 mol) of 6-(*o*-chlorophenyl)-2,4-hexanedione (1) in 125 ml of dry ether. The mixture was stirred an additional 1 hr and then neutralized with 13.40 g (0.25 mol) of solid NH_4Cl. The ammonia was evaporated as 250 ml of dry ether was added; this was followed by addition of 250 ml of 3 *N* HCl. The layers were separated, and the aqueous layer was extracted with three 100-ml portions of ether. The combined ether layers were dried ($MgSO_4$), filtered, and concentrated; an oil remained. The oil was shown to contain β-diketone 2 by conversion to its copper chelate, mp 228–230° (methanol) (lit.[2] mp 229–230.5°), and its pyrazole (49%), mp 136–138° (ether–ligroin) (lit.[2] 137–138°).

In one case, crystallization of the oil was effected upon prolonged standing (6–9 months), while other procedures failed to induce crystallization. After three recrystallizations from ethanol, 1-acetyl-2-tetralone (2), mp 73–76°, resulted: ir ($CHCl_3$) 1540, 760, and 700 cm^{-1}. This represented a 67% yield of 2.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.54; H, 6.43. Found: C, 76.44; H, 6.39.

The compound gave a violet ferric chloride test, and a pyrazole of 2 which was prepared in the standard manner had mp 136–138° after one recrystallization from ether–ligroin (lit.[2] 137–138°).

Conversion of 1 to Its Monoanion.—To a stirred solution containing 0.0915 mol of KNH_2 in 200 ml of NH_3 (l) and cooled by a Dry Ice–acetone bath and blanketed by nitrogen was added 22.45 g (0.10 mol) of 6-(*o*-chlorophenyl)-2,4-hexanedione (1) in 75 ml of dry ether. Some red coloration was noted.[5] The cooling was discontinued, and the mixture was stirred an additional 20 min. The ammonia was evaporated as 250 ml of dry ether was added, and *ca.* 100 g of crushed ice was slowly added, followed by 30 ml of cold concentrated HCl. The layers were separated, and the aqueous layer was extracted with two 100-ml portions of ether; the combined ether layers were dried ($MgSO_4$). After filtration, the solvent was evaporated to give an essentially quantitative (>95%) recovery of starting material. Similar results were observed when the solution of base was added to a cooled (−78°) solution of 1 from an inverse addition flask, the difference being less coloration.

Conversion of 1 to Its Dianion.—The procedure for conversion of 1 to its dianion was the same as previously described for the conversion of 1 to its monoanion, except that the KNH_2 was prepared from twice the amount of potassium, 7.13 g (0.183 g-atom). Only starting material 1 was found in the final residue.

Condensation of Dianion of 1 with Benzophenone.—Potassium amide was prepared in a 250-ml inverse addition flask from 2.15 g (0.055 g-atom) of potassium in 125 ml of anhydrous NH_3(l). The base was then added to a well-stirred solution of 5.61 g (0.025 mol) of 6-(*o*-chlorophenyl)-2,4-hexanedione (1) in 25 ml of dry ether. Upon completion of the addition a red-brown color resulted, and after stirring for 20 min, 4.55 g (0.025 mol) of benzophenone dissolved in 20 ml of dry ether was added; the mixture was stirred for 3 hr. The mixture was then inversely neutralized by pouring the reaction mixture into a large flask containing an excess of NH_4Cl dissolved in 100 ml of anhydrous NH_3(l). The ammonia was replaced by an equal volume of dry ether, and 200 ml of a 10% HCl soln was added. After separation of the layers, the aqueous layer was further extracted with three 75-ml portions of ether and the combined ether extracts were dried ($MgSO_4$). After filtration and evaporation of the solvent, 20–30 ml of absolute ethanol was added, and upon shaking a solid crystallized. After recrystallization from absolute ethanol, 4.00 g (41%) of 7-(*o*-chlorophenyl)-1,1-diphenyl-3,5-heptanedione-1-ol (5), mp 92–94°, was obtained: ir ($CHCl_3$) 3400, 1600, 1160, 755, 700 cm^{-1}; nmr ($CDCl_3$) δ 2.48–3.13 (m, 4 H, $-CH_2CH_2-$), 3.22 (s, 2 H, $-CH_2-$), 5.38 (s, 1 H, C_4 H_{enol}), and 7.00–7.50 (m, 14 H, Ar–H).

Anal. Calcd for $C_{25}H_{23}ClO_3$: C, 73.79; H, 5.70; Cl, 8.71. Found: C, 73.85; H, 5.67; Cl, 8.53.

Dehydration of 5 to Give β-Diketone–Olefin 6.—To a 1.0-g (0.00246 mol) sample 5 was added 10 ml of acetic acid. The mixture was stirred and cooled in an ice bath, while 1.0 ml of concentrated H_2SO_4 was added dropwise. The ice bath was removed, and the mixture was allowed to warm to room temperature. After 30 min, complete solution was effected, and the mixture was poured into a stirred ice–water mixture. The paste which resulted was removed by filtration and allowed to stand overnight. The residue was taken up in absolute ethanol and filtered. Crystallization resulted after standing at 0° for several days. The crude product was recrystallized from ethanol to give 0.28 g (30%) of 7-(*o*-chlorophenyl)-1,1-diphenyl-1-heptene-3,5-dione (6): mp 72–73.5°; ir ($CHCl_3$) 3077, 2433, 1618–1563, and 930 cm^{-1}; nmr ($CHCl_3$) δ 2.30–2.99 (m, 4 H, $-CH_2CH_2-$), 5.25 (s, 1 H, C_4 H_{enol}), 6.38 (s, 1 H, C_2 H), and 7.09–7.50 (m, 14 H, Ar–H).

Anal. Calcd for $C_{25}H_{21}ClO_2$: C, 77.21; H, 5.44; Cl, 9.12. Found: C, 77.12; H, 5.44; Cl, 9.12.

Preparation of the Dianion of 1-Acetyl-2-tetralone (2) and Condensation with Benzophenone to Form 7.—A 0.0478-mol solution of $NaNH_2$ in 500 ml of anhydrous NH_3(l) was prepared in a 1-l, inverse addition flask. This slurry was added to a stirred solution of 4.10 g (0.0218 mol) of 1-acetyl-2-tetralone (2) in 50 ml of dry ether. After 20 min, 3.96 g (0.0218 mol) of benzophenone was added, and the mixture was stirred an additional 20 min. The mixture was then inversely neutralized as previously described for 5, and the ammonia was replaced by 250 ml of dry ether. This was followed by the addition of 250 ml of water; the layers were separated. The aqueous layer was extracted with two 50-ml portions of ether, the combined ether extracts were dried (Na_2SO_4), filtered, and concentrated, and the residue was distilled to give 7 as a red liquid (73%), bp 161–165° (12 mm).

Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.05; H, 5.99. Found: C, 81.05; H, 5.92.

Carbinol–β-diketone 11 was found to undergo dehydration upon prolonged standing (1 year). An ir spectra of the resulting oil lacked hydroxyl absorption in the region 3300–3500 cm^{-1}, and, when the oil was treated with an ethanolic solution of hydrazine, the pyrazole of 7, mp 158–160° (methanol), was obtained in good yield.

Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.17; H, 5.78. Found: C, 86.11; H, 5.84.

Preparation of 5-(*o*-Chlorophenyl)-1-phenyl-1,3-pentanedione (8).—5-(*o*-Chlorophenyl)-1-phenyl-1,3-pentanedione (8), bp 173° (0.07 mm), was prepared in 73% yield from reaction of 29.1 g (0.180 mol) of *o*-chlorobenzyl chloride with the dicarbanion of benzoylacetone prepared from reaction of 34.74 g (0.213 mol) of

(4) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 122 (1954).

(5) In a control experiment, 0.10 mol of 6-phenyl-2,4-hexanedione was added to a solution containing 0.0915 mol of KNH_2 in NH_3 (l) and no coloration was observed. 6-Phenyl-2,4-hexanedione was recovered nearly quantitatively after neutralization.

benzoylacetone and 0.430 mol of $NaNH_2$ in NH_3 (l). This procedure is analogous to that described for chloro β-diketone **1**.

Anal. Calcd for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.22; Cl, 12.36. Found: C, 71.11; H, 5.33; Cl, 12.26.

The absorption spectra for **8** contained the following: ir 3106, 2950, 1618, 1055, 756, and 694 cm^{-1}; nmr δ 2.40–3.21 (m, 4 H, $-CH_2CH_2-$), 6.0 (s, 1 H, C_2 H_{enol}), and 6.9–7.8 (m, 9 H, Ar–H).

The pyrazole of **8** was prepared in the standard manner and was recrystallized from methanol, mp 99–101°.

Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.17; H, 5.34; Cl, 12.53; N, 9.95. Found: C, 72.43; H, 5.45; Cl, 12.76; N, 9.86.

Registry No.—**2**, 24118-62-5; **5**, 24118-63-6; **6**, 24118-64-7; **7**, 24118-65-8; **8**, 24118-66-9; pyrazole of **7**, 24110-98-3; pyrazole of **8**, 24118-71-6.

Coupling of Carbanions. Formation of Succinic Acid Derivatives

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Alkali metal diphenylmethides have previously been shown to react with certain polyhalides by a displacement on halogen to give the dehalogenation product from the halide and a benzhydryl halide.[1] While the halogenated compound has been isolated from the reaction with carbon tetrachloride,[2] under the usual reaction conditions (addition of halide to anion) it reacts further with the anion to give tetraphenylethane (Scheme I).

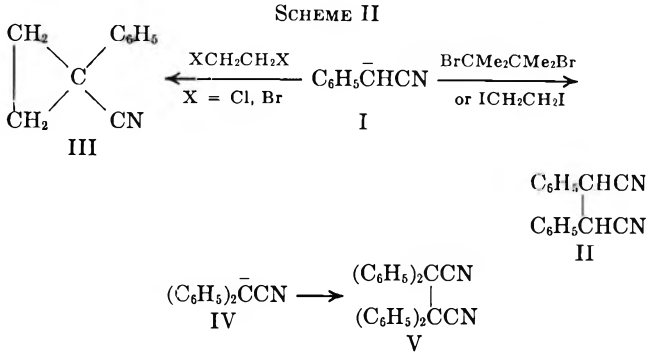
SCHEME I

$$(C_6H_5)_2CH_2 \xrightarrow{KNH_2} (C_6H_5)_2\bar{C}H \xrightarrow{X\text{-}C\text{-}C\text{-}X} (C_6H_5)_2CHX \xrightarrow{(C_6H_5)_2\bar{C}H} (C_6H_5)_2CHCH(C_6H_5)_2$$

Several such reactions to give halogen compounds from carbanions have been reported.[3] We now report the synthetic utility of this reaction in the coupling of anions from nitriles and esters to give succinic acid derivatives.

Phenylacetonitrile and Diphenylacetonitrile.—Potassio- and sodiophenylacetonitrile (I), prepared from the nitrile and potassium or sodium amide, was previously shown to undergo generally twofold alkylation with alkyl halides.[4] Thus reaction with ethylene chloride gives equal amounts of 1-phenylcyclopropanecarbonitrile (III) and phenylacetonitrile. It was previously shown that ethylene iodide and ethylene bromide react with potassium diphenylmethide by displacement on halogen to give the dimeric product (tetraphenylethane), while ethylene chloride undergoes twofold alkylation to give 1,1,4,4-tetraphenylbutane.[1] In agreement with this, ethylene iodide reacts with I to give the dimer, 2,3-diphenylsuccinonitrile (II), but ethylene bromide *does not* effect dimerization, and, like ethylene chloride, undergoes twofold alkylation (see Scheme II). In none of the cases studied did

SCHEME II



2,3-dibromo-2,3-dimethylbutane, a ditertiary halide, undergo alkylation.

The yields of II in the dimerization reactions were difficult to reproduce, apparently because this nitrile can undergo dehydrocyanation with potassium amide or other anion.[5] Such a dehydrocyanation is not possible with dimer V, which was obtained from potassiodiphenylacetonitrile (IV) in 85% yield even when the direct addition procedure was employed.

Ethyl Phenylacetate and Ethyl Diphenylacetate.—The potassium derivatives of these esters were readily prepared from the esters and ammoniacal potassium amide. The product from the latter ester, diethyl tetraphenylsuccinate, was not obtained crystalline and was identified by hydrolysis to the acid (see Scheme III). The yields of these reactions are summarized in Table I.

SCHEME III

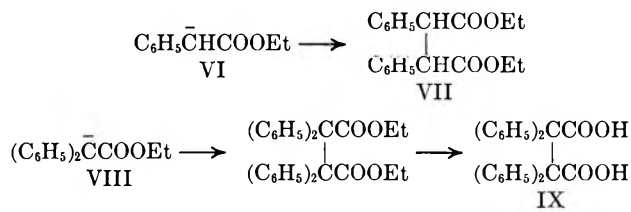


TABLE I

DIMERIZATION OF ANIONS OF ESTERS AND NITRILES

Anion (mol)	Halide (mol)	Product (yield, %)
I (0.05)	$BrCMe_2CMe_2Br$ (0.025)	II (16, *meso;* 37, *dl*) CN^- (22)
I (0.05)	$BrCMe_2CMe_2Br$ (0.025)[a]	II (6, *meso;* 63, *dl*)
I (0.1)	$BrCH_2CH_2Br$ (0.05)	Phenylacetonitrile (92) III (91)
I (0.05)	ICH_2CH_2I (0.025)	II (33)
I (0.1)	Cl_3CCCl_3 (0.05)	II (5, *meso;* 45, *dl*)
IV (0.05)	$BrCMe_2CMe_2Br$ (0.025)	V (85)
VI (0.08)	$BrCMe_2CMe_2Br$ (0.04)	VII (36)
VI (0.1)	Cl_3CCCl_3 (0.05)	VII (54, *meso;* 24, *dl*)
VIII (0.05)	$BrCMe_2CMe_2Br$ (0.025)	IX (54)

[a] The inverse addition procedure was employed.

(1) W. G. Kofron and C. R. Hauser, *J. Amer. Chem. Soc.*, **90**, 4126 (1968).
(2) W. G. Kofron and C. R. Hauser, *J. Org. Chem.*, **28**, 577 (1963).
(3) F. H. Rash, S. Boatman, and C. R. Hauser, *J. Org. Chem.*, **32**, 372 (1967); R. L. Gay, T. F. Crimmins, and C. R. Hauser, *Chem. Ind.* (London), 1635 (1966).
(4) C. R. Hauser and W. R. Brasen, *J. Amer. Chem. Soc.*, **78**, 494 (1956).
(5) For related dehydrocyanations, see C. R. Hauser and W. R. Brasen, *ibid.*, **78**, 82 (1956).

Experimental Section

Formation and Coupling of Carbanions.—The anions were prepared by addition of an ethereal solution of the ester or nitrile to 1 equiv of potassium amide in 120–200 ml of liquid ammonia and stirring for 20 min. An ethereal solution of the halide (0.5 molar equiv) was added, the ammonia was allowed to evaporate, and the residue was stirred with water and ether or chloroform and filtered. Individual work-ups follow.

2,3-Diphenylsuccinonitrile (II).—The solid on the funnel was recrystallized from acetic acid to give tan needles of the *meso* nitrile, mp 238° (lit.[6] mp 239–240°). The chloroform solution was diluted with ethanol and chilled, giving the *dl* nitrile, mp 164° (lit.[6] mp 164°). The aqueous solution gave a positive Prussian Blue test for cyanide, which was quantitatively determined.[7]

Tetraphenylsuccinonitrile (V).—The chloroform solution was evaporated, and the residue was recrystallized from chloroform–ethanol to give tetraphenylsuccinonitrile, mp 215°, undepressed by an authentic sample.[8]

Diethyl 2,3-Diphenylsuccinate (VII).—The solid on the funnel was recrystallized from aqueous methanol to give the *meso* ester, mp 140–141° (lit.[9] mp 140–141°). The ethereal solution was evaporated, and the residue was recrystallized from aqueous methanol to give the *dl* ester, mp 79–80° (lit.[9] mp 82–82.5°).

Tetraphenylsuccinic Acid.—Evaporation of the ethereal solution gave an oily solid which several recrystallizations failed to purify. The material was hydrolyzed overnight in refluxing ethanol with 5.7 g (0.1 mol) of potassium hydroxide. The ethanol was evaporated, and the residue was stirred with water and methylene chloride. The aqueous solution was acidified, and the tetraphenylsuccinic acid was recrystallized from methylene chloride–ethanol to give white crystals, mp 271° dec (lit.[10] mp 260–262°).

Reaction of I with Ethylene Bromide.—Evaporation of the ethereal solution gave 21.5 g of a yellow-brown oil, shown by nmr to be a mixture of phenylacetonitrile and 1-phenylcyclopropanecarbonitrile. The mixture was not separated by distillation through a 6 in. helix-packed column, but was satisfactorily separated by gas chromatography (1-m column, 20% methyl silicone SE-30). The nmr spectrum of a sample of pure III, collected from the gas chromatograph, was identical with the published spectrum.[11] The relative yields of the two nitriles (Table I) were estimated from the ratio of the peak areas.

Registry No.—*meso*-II, 15146-07-3; *dl*-II, 19657-49-9; III, 935-44-4; V, 3122-21-2; *meso*-VII, 13638-89-6; *dl*-VII, 24097-93-6; IX, 24097-49-2.

Acknowledgment.—This work was supported at the University of Akron by a grant from the Petroleum Research Fund, administered by the American Chemical Society, and at Duke University by the National Science Foundation.

(6) L. Chalanay and E. Knoevenagel, *Ber.*, **25**, 289 (1892).
(7) F. Charlot and D. Bezier, "Quantitative Inorganic Analysis," translated by R. C. Murray, John Wiley & Sons, New York, N. Y., 1957, p 380.
(8) K. Auwers, and V. Meyer, *Ber.*, **22**, 1227 (1889).
(9) H. Wren and C. J. Still, *J. Chem. Soc.*, 444 (1915).
(10) H. Bickel, *Ber.*, **22**, 1537 (1889).
(11) A. A. Pavia, J. Wylde, E. Arnal, and B. Filliatre, *Bull. Soc. Chim. Fr.*, 460 (1964).

The *A* Value of Hydroxyl Determined by the Nuclear Magnetic Resonance Peak Area Method at −83°

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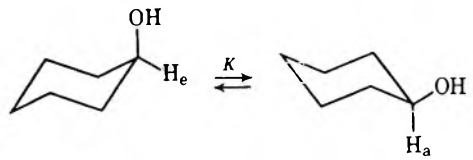
A myriad of reports have appeared concerning the measurement of the *A* value of hydroxyl (eq 1 and 2)



(1)

$$A \text{ value} = -\Delta G^\circ = (RT \ln K)/1000 \quad (2)$$

employing a large variety of techniques.[2–4] The observed *A* values are solvent dependent but deviate seriously from one technique to another in the same solvent.[2] This paper concerns the measurement of the *A* value of hydroxyl in cyclohexanol-2,2,6,6-d_4 at −83° utilizing variable-temperature nuclear magnetic resonance (nmr) spectroscopy, a technique of proven accuracy.[3]

Examination of the nmr spectrum (60 MHz) of cyclohexanol-2,2,6,6-d_4 at −83° in a number of solvents revealed two resonances corresponding to the equatorial HCO proton (H_e, eq 1) at approximately δ 3.85 and to the axial HCO proton (H_a, eq 1) at approximately δ 3.28 (Figure 1). These peak assignments are consistent with those in model compounds[5] and were confirmed by deuteration of the hydroxyl group and investigation of the HCO resonance under conditions of slow, intermediate, and fast rates of exchange on the nmr time scale.

Integration by planimeter and electronic integrator of the peak areas of axial and equatorial HCO resonances at −83° gave the equilibrium constant (*K*, eq 1) of interest and the corresponding *A* values in a variety of solvents (Table I). Since the measured equilibrium constants (*K*, eq 1) are relatively large by nmr standards, a correspondingly large radiofrequency power level was necessary to obtain reasonable reproducibility in peak areas. This introduces the possibility of differential saturation effects on the two H–C–O resonances, but these effects are included in the error limit set on *K* (eq 1, Table I).

Table I
A Value of Hydroxyl as a Function of Concentration and Solvent at −83°

Group	Solvent	Concn, mol/l.	*K*	*A* value, kcal/mol
-OH	CS_2	3.0	17.0 ± 1.0	1.08 ± 0.06
		2.0	12.9 ± 0.7	0.97 ± 0.05
		1.0	11.6 ± 0.8	0.93 ± 0.05
		0.5	11.3 ± 0.8	0.92 ± 0.05
-OD	CS_2	2.0	11.6 ± 0.8	0.93 ± 0.05
-OH	Toluene	2.0	11.3 ± 0.8	0.92 ± 0.05
	Toluene	1.0	11.0 ± 0.8	0.91 ± 0.05
-OH	CD_3COCD_3	1.0	12.9 ± 0.9	0.97 ± 0.05
-OH	50% CS_2	2.0	11.6 ± 0.6	0.93 ± 0.05
	50% α-picoline	1.0	11.5 ± 0.7	0.93 ± 0.05
	(by wt)	0.5	11.5 ± 1.8	0.92 ± 0.06
-OD	CD_3OD	1.0	16.1 ± 1.0	1.05 ± 0.06
	CD_3OD	2.0	15.8 ± 1.0	1.04 ± 0.06

(1) National Science Foundation Undergraduate Research Participant, Summer 1969.
(2) J. A. Hirsch, *Top. Stereochem.* **1**, 199 (1967), and references therein.
(3) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, **91**, 344 (1969).
(4) G. Ransbotyn, R. Cttinger, J. Reisse, and G. Chiurdoglu, *Tetrahedron Lett.*, 2535 (1968).
(5) J. Reisse, J. C. Celotti, D. Zimmermann, and G. Chiurdoglu, *ibid.*, 2145 (1964).

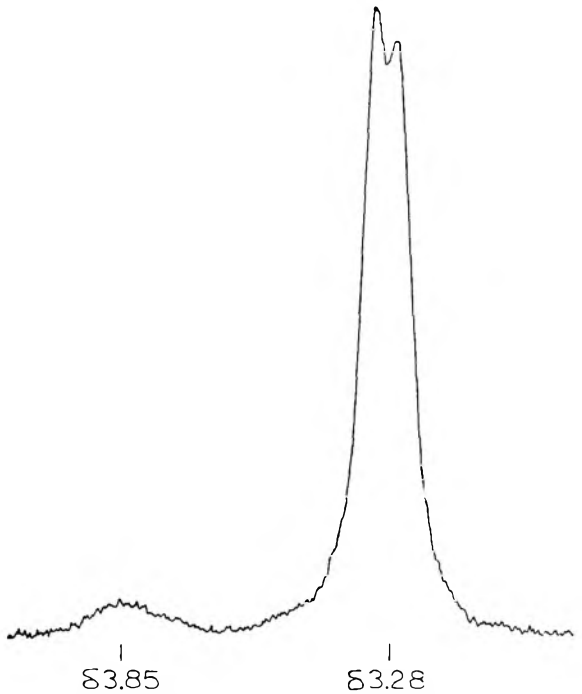


Figure 1.—Axial (δ 3.28) and equatorial (δ 3.85) HCO resonances of cyclohexanol-2,2,6,6-d_4 (3 *M* in CS_2) at −83°.

Perusal of Table I indicates no dramatic solvent effects (in the solvents used) although some variation is noted. The *A* value of hydroxyl is larger in the hydroxylic solvent CD_3OD, as expected. Some error is introduced into the *A* value determined in CD_3OD because of a slight overlap of the CHD_2OD impurity resonance with the axial H–C–O resonance of cyclohexanol-2,2,6,6-d_4.

These data provide an opportunity for a meaningful comparison albeit at a low temperature of the *A* value of hydroxyl with other oxygen-containing functionalities (Table II). Although the effective group radius of hydroxyl is almost certainly smaller than the other functionalities, it has a significantly higher *A* value. The effect of intermolecular association is evident. It is also clear from Table II that the *A* values of functionalities with oxygen bonded to the cyclohexane ring are not all of the same magnitude.

TABLE II

A VALUES OF VARIOUS OXYGEN-CONTAINING FUNCTIONALITIES

Group	*A* value, kcal/mol[a]	Group	*A* value, kcal/mol[a]
-OTs	0.52	-OC(=O)H	0.59
$-OCD_3$	0.55	-OAc	0.71
$-OSO_2CH_3$	0.56	-OH	0.97[b]

[a] All concentrations approximately 2 *M*. Solvent is CS_2 except for OTs and OSO_2CH_3 in which case it is approximately 50:50 by volume CS_2–$CDCl_3$; see ref 3. [b] This work.

Experimental Section

Nmr spectra were obtained using a Varian HR-60A spectrometer equipped with a custom-built variable-temperature probe. Spectral calibrations were performed using the audio-modulation technique. Temperature measurements were performed using a calibrated copper-constantan thermocouple.

Cyclohexanol-2,2,6,6-d_4 was prepared by the lithium aluminum hydride reduction of cyclohexanone-2,2,6,6-d_4.[6]

Registry No.—Cyclohexanol-2,2,6,6-d_4, 21273-03-0.

Acknowledgment.—We thank Research Corporation (Cottrell Grant) and the National Science Foundation (COSIP Grant) for support of this work.

(6) E. Premuzic and L. W. Reeves, *Can. J. Chem.*, **40**, 1870 (1962).

Biosynthetic Studies with Carbon 13. Piericidin A

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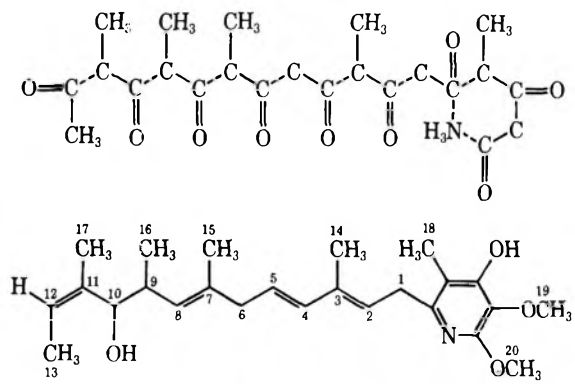
Received November 10, 1969

The antibiotic piericidin A is a naturally occurring insecticide which is produced by *Streptomyces mobaraensis*.[1] Its structural and stereochemical formulation (I) is due to the work of Takahashi and coworkers.[2] Biosynthetic studies conducted with carbon 14 labeled precursors indicated that the carbon chain of Piericidin A is formally derived by condensation of five propionate and four acetate units, presumably *via* an acetate starter and the methylmalonyl pathway.[3] A useful procedure for biosynthetic studies of microbial metabolites is the nondegradative ^{13}C proton satellite method.[4] We wish to report that the production of piericidin A in the presence of ^{13}C-methyl labeled propionate ($^{13}CH_3CH_2CO_2Na$) affords direct information on the biological origin of the methyl groups in the antibiotic. This information can be obtained by the ^{14}C method; however, limitations on chemical degradative methods preclude identification of specific labeled carbon atoms.



I

Streptomyces mobaraensis fermentations in the pre-

(1) S. Tamura, N. Takahashi, S. Miyamoto, R. Mori, S. Suzuki, and J. Nagatsu, *Agr. Biol. Chem.* (Tokyo), **27**, 576 (1963).

(2) (a) N. Takahashi, A. Suzuki, and S. Tamura, *J. Amer. Chem. Soc.*, **87**, 2066 (1965); (b) N. Takahashi, A. Suzuki, and S. Tamura, *Agr. Biol. Chem.* (Tokyo), **30**, 1 (1966); (c) N. Takahashi, S. Yoshida, A. Suzuki, and S. Tamura, *ibid.*, **32**, 1108 (1968).

(3) (a) N. Takahashi, Y. Kimura, and S. Tamura, *Tetrahedron Lett.*, 4659 (1968); (b) Y. Kimura, N. Takahashi, and S. Tamura, *Agr. Biol. Chem.* (Tokyo), **33**, 1507 (1969).

(4) (a) M. Tanabe and G. Detre, *J. Amer. Chem. Soc.*, **88**, 4515 (1966); (b) D. Desaty, A. G. McInnes, D. G. Smith, and L. C. Vining, *Can. J. Biochem.*, **46**, 1293 (1968). (c) A. G. McInnes, D. G. Smith, L. C. Vining, and J. L. C. Wright, *Chem. Commun.* 1669 (1968).

viously reported C[4] medium[1] supplemented with 56% $^{13}CH_3CH_2CO_2Na$ (100 mg/40 ml) yielded after a 24-hr incubation isotopically enriched piericidin A. In the nmr spectrum of piericidin A, the C_{14}, C_{15}, C_{16}, C_{17}, and C_{18} methyl resonances are resolved and their positions can be assigned,[2c] thereby allowing most of their corresponding satellites in the labeled compound to be readily located and identified, and their intensities measured. The source of the methoxyl groups in the antibiotic was determined by additional experiments with 56% enriched [$^{13}CH_3$]-methionine (100 mg/40 ml). The nmr data for the labeled piericidins are summarized in Table I.

TABLE I

NMR DATA FOR PIERICIDIN A

			—100-MHz yield[a]—		—60-MHz yield—	
	τ	J^{13}_{CH}, Hz	Upfield satellite	Downfield satellite	Upfield satellite	Downfield satellite
			^{13}C-Propionate			
C_{14} CH_3	8.20	126	8.7[b]	10.1[c]	*d*	*e*
C_{15} CH_3	8.36	124	*d*	10.5[c]	9.8	*e*
C_{16} CH_3	9.18	128	9.6	*f*	12.4	*d*
C_{17} CH_3	8.24	126	7.3[b]	10.5[c]	*e*	*e*
C_{18} CH_3	7.90	130	9.1[g]	*e*	10.2	8.7
			^{13}C-Methionine			
C_{19} OCH_3	6.04	147	15.3	17.3		
C_{20} OCH_3	6.14	146	17.2	17.2		

[a] The yields are expressed a atom per cent excess ^{13}C. The incorporation yields were determined by comparing the area of the satellite peak with the area of the unlabeled carbon-1 methylene protons as an internal standard. Yields represent the area determined *via* a single scan on the Varian HA-100 and A-60A, respectively. Incorporation values are ±15% error. [b] This is an approximate value, since an impurity peak gives an overlapping signal at τ 8.75. [c] Spin decoupling proved that the C_9 proton which appears in this region of the spectrum, does not overlap with this downfield satellite peak. [d] This satellite signal was observed; however, owing to an impurity signal and/or overlapping signals, this yield was not calculated. [e] This satellite signal was completely obscured by overlapping signals. [f] This downfield satellite signal overlapped the upfield satellite signal of the C_{18} CH_3 group. [g] This signal appeared at τ 8.6 together with the C_{16} CH_3 downfield signal. This yield was approximated by subtracting the upfield C_{16} CH_3 area from the total peak area.

These data unequivocally show that five C-methyl groups are biosynthetically derived from the methyl group of propionate and the terminal C_{13} methyl group is not propionate derived. The nearly equal labelling pattern observed in the methyl groups along the chain implies that only a single polyketide chain is assembled subsequent to nitrogen introduction to form the pyridine ring. No other biogenetic unit appears to be involved. These results amplify and are in accord with the ^{14}C biosynthesis work.

We observed that incorporation of [$^{13}CH_3$]-methylmalonic acid into piericidin A was very low, since satellite bands could not be observed with a single scan. The poor incorporation is probably due to a cell membrane permeability effect. A similar result was observed in the biosynthesis of erythromycin.[5]

The general use of $^{13}CH_3CH_2CO_2Na$ and nmr for establishing the origin of methyl groups derived from propionate in microbial metabolites is a useful technique and high incorporation yields can be generally anticipated. The method is a useful complement to the radio carbon method.

(5) S. M. Friedman, T. Kaneda, and J. W. Corcoran, *J. Biol. Chem.*, **239**, 2396 (1964).

Registry No.—Piericidin A, 24467-35-4.

Acknowledgment.—We thank Professor N. Takahashi for the culture of *Streptomyces mobaraensis*, a sample of piericidin A, and helpful exchange of information, and R. Dehn for the synthesis of the carbon-13 labeled substrates. This work was supported by the U. S. Public Health Service Grant No. AI 08143.

Diels–Alder Reaction of Tetrachloroethylene with Anthracene

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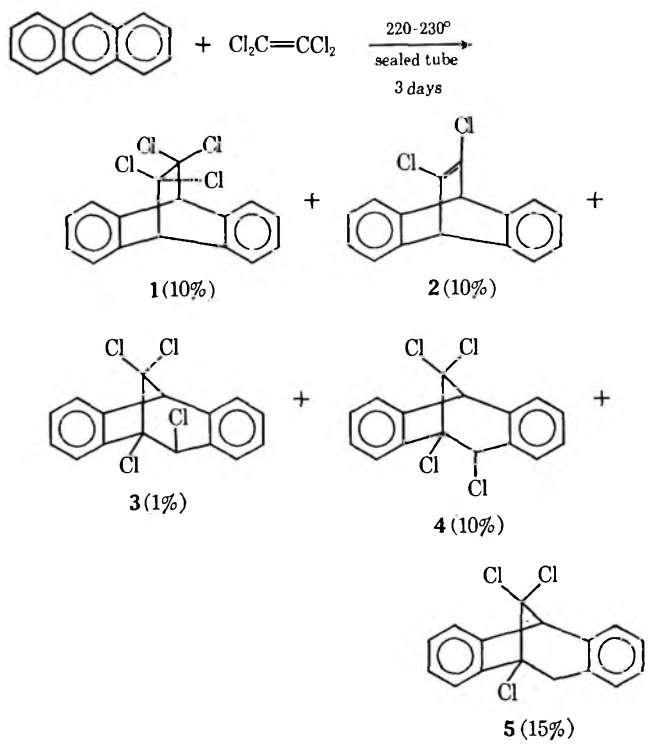
In connection with other experiments we wished to synthesize 11,11,12,12-tetrachloro-9,10-dihydro-9,10-ethanoanthracene (**1**). The only mention in the literature of this compound is the report of Russian workers[1,2] that **1** results from the Diels–Alder reaction of tetrachloroethylene with anthracene. We have repeated



this reaction and find that indeed **1** (mp 205–206°) is produced, albeit in a mixture with a number of other compounds. One of these other characterizable products is 11,12-dichloro-9,10-dihydro-9,10-ethenoanthracene (**2**), which from the melting point (179–180°) appears to be the compound the earlier workers assigned as **1**. The conclusion is supported by dipole-

(1) V. M. Zonoastrova and B. A. Arbuzov, *Dokl. Akad. Nauk SSSR*, **60**, 59 (1948).

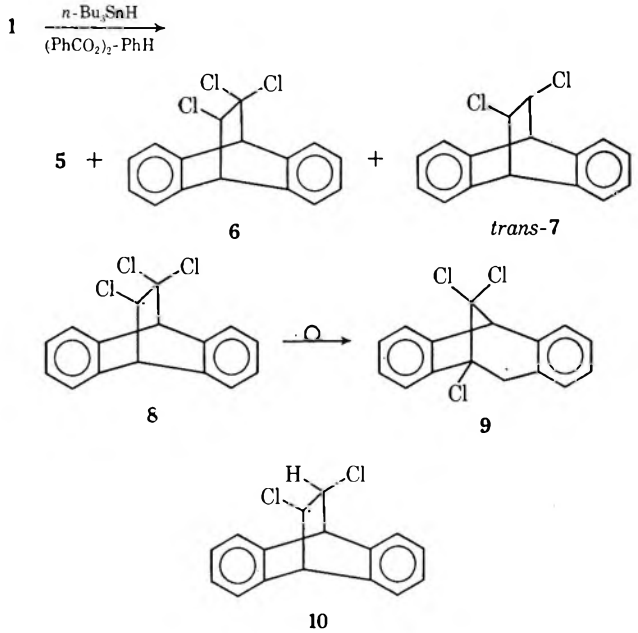
(2) B. A. Arbuzov and A. N. Vereshchagin, *Bull. Acad. Sci. USSR*, 936 (1964).

moment studies[2] on the compound isolated by the Russians; the observed dipole moment for the Russians' compound (mp 178–180°) is 2.09 D, a value more in agreement with structure 2.

The Diels–Alder reaction of tetrachloroethylene and anthracene yields three other compounds in addition to 1 and 2 plus large amounts of tars. Compounds 3 and 4 were synthesized in high yields from the ionic addition of chlorine to 2 in nitromethane (3 isomerizes to 4 when allowed to stand under these reaction conditions for longer periods of time; similar isomerizations have been observed previously)[3] while the free-radical addition of chlorine to 2 in carbon tetrachloride gives 1 in quantitative yield.[4] Treatment of 3 and/or 4 with hydrogen in the presence of 10% Pd–C converts these compounds to 5.

If the Diels–Alder reaction is run at 210° for 2 days, one obtains the normal addition product 1 with only small amounts of side products; however, the reaction occurs only to a small extent, and large amounts of unreacted anthracene result. When the tetrachloride 1 is heated (neat) in a sealed tube at 230° for 1 day, it is partially converted to 4. (When 3 is heated under these conditions, it is >90% converted to 4.) If this reaction is run in the presence of anthracene, 5 also is observed among the products. What appears to be happening is that 1 loses chlorine at high temperature to give 2 which then undergoes ionic addition of chlorine to give the rearranged chlorides 3 and 4. In the presence of anthracene, chlorine reacts to give 9,10-dichloro-9,10-dihydroanthracene which would be expected to lose hydrogen chloride readily (accounting for the hydrogen chloride observed in this reaction; see Experimental Section) to give 9-chloroanthracene.[6] 9,10-Dichloro-9,10-dihydroanthracene might also act as a source of hydrogen atoms for the reduction of 3 and/or 4 to 5. We have tested this by heating a mixture of 3 and 4 with 9,10-dihydroanthracene (230°, 1 day) and find that 3 and 4 are completely hydrogenolyzed to 5. Similar treatment of the tetrachloride 1 with 9,10-dihydroanthracene apparently also gives 5, but this reaction yields a large number of unidentifiable products.

The trichloride 5 also is produced in the reaction of 1 with tri-*n*-butyltin hydride (*n*-Bu_3SnH) in refluxing benzene, a type of reaction known[7] to proceed *via* a free-radical mechanism. The relative amount of 5 increases with increasing dilution of *n*-Bu_3SnH, a fact consistent with a rearrangement[8] of radical 8 to the more stable benzylic radical 9 followed by chain transfer with *n*-Bu_3SnH to give 5. Reduction of 1 with a relatively high concentration of *n*-Bu_3SnH yields only 6. When 6 is allowed to react with *n*-Bu_3SnH under these conditions, only *trans*-7 results, and no products arising from rearrangement are observed even at high dilution. The fact that 8 rearranges while the radical 10 does not is probably due to the increased steric inhibition to chain transfer caused by the presence of two β-chlorine atoms in radical 8 compared with only one β-chlorine atom in radical 10.[9]



Experimental Section[13]

Preparation of 11,11,12,12-Tetrachloro-9,10-dihydro-9,10-ethanoanthracene (1) by Diels–Alder Reaction with Anthracene.—Into a 26-in. thick-walled glass tube were placed 20 g (0.11 mol) of purified anthracene, 70 ml of tetrachloroethylene (0.683 mol), and 0.5 g of 4-*t*-butylpyrocatechol. The sealed tube was placed in a heater for 2.5 days with the temperature maintained at 220–230°. *Caution:* Upon opening there may be pressure due to HCl gas. The reaction solution was transferred to a 500-ml round-bottom flask with methylene chloride and the volatile solvents were removed by rotary evaporation. To the round-bottom flask were added 15.0 g (0.153 mol) of maleic anhydride and 100 ml of *p*-xylene. The mixture was stirred at reflux for 4 hr after which the warm solution was filtered and the *p*-xylene removed by rotary evaporation. The resulting crude product was taken up in 200 ml of ether and extracted twice with 100-ml portions of saturated sodium carbonate solution. The ether layer was dried over magnesium sulfate and the ether removed by rotary evaporation to give 18 g of crude oil.

The crude product was placed, using a minimum amount of carbon tetrachloride, on a 5-ft chromatography column containing 400 g of Fischer silica gel. The column was eluted with 5% benzene–95% Skellysolve B. First off the column was 2 (3 g, 10%), mp 179–180°,[5] followed by a mixture of 1 (3.8 g, 10%), mp 204–205°, *endo*-4-chloro-5,8,8-trichlorodibenzobicyclo[3.2.1]-octadiene (4) (3.4 g, 10%), mp 135–136°, and 5,8,8-trichlorodibenzobicyclo[3.2.1]octadiene (5) (4.5 g, 15%), mp 124–125°. There were traces of *exo*-4-chloro-5,8,8-trichlorodibenzobicyclo-[3.2.1]octadiene (3) (*ca.* 1%), mp 147–148.5°, in the last fractions

(3) S. J. Cristol and B. B. Jarvis, *J. Amer. Chem. Soc.*, **88**, 3091 (1966).

(4) This in fact proves to be the best procedure for obtaining 1 or 3 and 4, since 2 can be made in high yield from 11,11,12-trichloroethanoanthracene by treatment with potassium *t*-butoxide in dimethyl sulfoxide.[5]

(5) B. B. Jarvis, Ph.D. Thesis, University of Colorado, 1966.

(6) Careful work-up of this reaction mixture does indeed yield a small amount (isolated by glpc) of 9-chloroanthracene.

(7) D. J. Carlsson and K. V. Ingold, *J. Amer. Chem. Soc.*, **90**, 7047 (1968).

(8) C. Walling in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963 Chapter 7.

(9) Free-radical phenyl migrations seldom have been observed in bridged bicyclic systems.[10] A number of free-radical additions to 9,10-dihydro-9,10-ethenoanthranes have been reported,[11,12] but no products arising from free-radical rearrangements were observed. We have investigated the free-radical additions of carbon tetrahalides to a number of 11-substituted 9,10-dihydro-9,10-ethenoanthracenes and find that extensive rearrangements of the intermediate radicals do occur and in a rather stereoselective manner. These results will be reported shortly.

(10) S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.*, **32**, 3727 (1967).

(11) S. J. Cristol, R. Caple, R. M. Sequeira, and L. O. Smith, Jr., *J. Amer. Chem. Soc.*, **87**, 5679 (1965).

(12) B. B. Jarvis, *J. Org. Chem.*, **33**, 4075 (1968).

(13) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Proton magnetic resonance spectra were measured in carbon tetrachloride solutions with a Varian A-60D pmr spectrometer with tetramethylsilane (τ 10.00) as an internal standard. Infrared spectra were measured in carbon tetrachloride solution on a Beckman IR-8 infrared spectrometer. Elemental analyses were performed by Dr. F. J. Kasler, University of Maryland.

collected. All fractions were weighed and analyzed by thin layer chromatography, pmr spectra, and ir spectra. All the above products except **3** were isolated and their structures characterized by pmr and ir spectra, melting points, and carbon–hydrogen analyses.

Outside the aromatic region, the pmr spectra show (a) for **1** a singlet (2 H) at τ 5.14, (b) for **2** ($\nu_{C=C}$ at 1600 cm^{-1}) a singlet (2 H) at τ 5.03, (c) for **3** two singlets (1 H each) at τ 5.43 and 4.61, (d) for **4** two singlets (1 H each) at τ 5.44 and 4.31, (e) for **5** a singlet (1 H) at τ 5.44 and a pair of doublets (1 H each, J_{gem} = 16.5 Hz) at τ 6.67 and 6.18.

Anal. Calcd for $C_6H_{10}Cl_4$ (**1**): C, 55.85; H, 2.93. Found: C, 55.58; H, 3.03. Calcd for $C_{16}H_{10}Cl_4$ (**3**): C, 55.85; H, 2.93. Found: C, 55.87; H, 3.09. Calcd for $C_{16}H_{10}Cl_4$ (**4**): C, 55.85; H, 2.93. Found: C, 55.83; H, 3.05. Calcd for $C_{16}H_{11}Cl_3$ (**5**): C, 62.07; H, 3.58. Found: C, 62.09; H, 3.65.

A similar reaction of anthracene with tetrachloroethylene in a sealed tube at 210° for 2 days gave large amounts of recovered anthracene (*ca.* 80% recovery). Anthracene was separated from the crude reaction mixture (*via* crystallization and the formation of the maleic anhydride adduct of anthracene), and a pmr spectrum of the resulting mixture showed the presence of **1** with only trace amounts of other products. Chromatography over alumina gave **1** in *ca.* 5% yield.

Preparation of 3 and 4.—Dry chlorine gas was bubbled into a stirred solution of 10.0 g (36.6 mmol) of **2** in 50 ml of nitromethane until saturation was achieved. The reaction vessel was stoppered and wrapped in aluminum foil to prevent photoinitiated reactions from taking place. The reaction progress was followed by the disappearance of the double-bond absorption (1600-cm^{-1} band) in the ir spectrum. After standing at room temperature for 1 day, a 50:50 mixture (by pmr spectroscopy) of the two epimers **3** and **4** resulted. The crude product, 7.5 g of oil, was crystallized from ethanol to give 2.0 g (16% yield) of each epimer. The low yield was due to the difficulty involved in separating the two epimers. The epimers could also be separated by chromatography over silica gel (**4** is eluted first with 5% benzene in Skellysolve B).

Photochlorination of 2 to Give 1.—Dry chlorine gas was bubbled through a solution of 1.0 g (3.36 mmol) of **2** in 20 ml of carbon tetrachloride until the solution turned deep green. The reaction vessel was stoppered and set in the presence of a sun lamp for 5 hr, after which time the double bond absorption at the 1600-cm^{-1} band in the ir spectrum had disappeared. The carbon tetrachloride was removed by rotary evaporation and the remaining oil crystallized from Skellysolve B to give 1.1 g (87% yield) of **1**, mp 204–205°.

Preparation of 5.—The reaction vessel containing 3.0 g (8.7 mmol) of a 50:50 mixture of **3** and **4** in 50 ml of ethanol was placed in a Parr bomb hydrogenation apparatus and flushed several times with hydrogen gas. The mixture was allowed to react for 2.5 days at 40-psi hydrogen gas pressure. The catalyst was removed by filtration, and the ethanol was removed by rotatary evaporation to give an oil which was crystallized from methanol to give 1.0 g (35%) of 5,8,8-trichlorodibenzobicyclo-[3.2.1]octadiene (**5**), mp 124–125°.

Treatment of 1 and 3 and 4, under Diels–Alder Reaction Conditions.—In 0.5-in. medium-walled glass tubes were sealed (a) 0.35 g of **1**, (b) 0.38 g of **1** and 0.51 g of anthracene, (c) 0.43 g of a mixture of **3** (90%) and **4** (10%) and 0.25 g of 9,10-dihydroanthracene, and (d) 0.31 g of **1** and 0.28 g of 9,10-dihydroanthracene. These tubes were heated at 230° in a silicon oil bath for 1 day. The tubes were opened, and pmr spectra were taken of the resulting dark colored mixtures.

(a) The pmr spectrum showed **1** and **4** present in the ratio of 2:1, respectively. A trace of **3** also was discernible in the pmr spectrum. Isolation by chromatography gave 0.19 g (54%) of recovered **1** and 0.10 g (29%) of **4**.

(b) The pmr spectrum indicated the presence of **1**, **4**, and **5** but in admixture with a number of unidentifiable compounds. This mixture was worked up by chromatography over silica gel. The fractions containing anthracene were combined and analyzed by glpc [5-ft column with 20% SE-30 on Chromosorb W (60–80 mesh) at 200°]. The peak that corresponded to 9-chloroanthracene (ratio of anthracene to 9-chloroanthracene was *ca.* 20:1) was collected and shown to be 9-chloroanthracene by ir and mixture melting point with an authentic sample of 9-chloroanthracene.[14]

(14) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963).

(c) The pmr spectrum showed only anthracene and **5** present. These were separated by chromatography over silica gel to give 0.25 g (65%) of **5**.

(d) The pmr spectrum was similar to that of reaction b. No attempt was made to isolate the products.

Reduction of 1 with Tri-*n*-butyltin Hydride (Dilute Conditions).—To a solution of 0.5 g (1.45 mmol) of **1** in 50 ml of dry benzene at reflux was slowly added (under nitrogen) a solution of 0.411 g (1.42 mmol) of tri-*n*-butyltin hydride and 40 mg of benzoyl peroxide dissolved in 30 ml of dry benzene. Reflux was maintained for 14 hr. A pmr spectrum was taken which indicated the presence of **1** (10%), **6** (32%), **2** (*ca.* 1%), **7**[15] (15%), and **5** (42%). The solvent was removed and the oil placed on a chromatography column containing 25 g of Fischer absorption alumina. The column was eluted with 3% benzene–97% Skellysolve B. Partial separation was achieved by this method. First off the column was a mixture of **2** and **5** followed by **2** and then a second mixture of **1** and **6**. The fractions collected were analyzed by thin layer chromatography and pmr spectroscopy.

Reduction of 1 with Tri-*n*-butyltin Hydride (Concentrated Conditions).—A solution of 30 ml of dry benzene, 0.50 g (1.45 mmol) of **1**, 0.67 g (2.3 mmol) of *n*-BuSnH, and 40 mg of benzoyl peroxide were held at reflux (under nitrogen). After 11 hr at reflux the solution was concentrated, and a pmr spectrum indicated the presence of *n*-Bu_3SnCl and a mixture of **6**[1] (80%) and **7**[12] (20%).

Reduction of 6 with Tri-*n*-butyltin Hydride.—Similar treatment of **6** with *n*-Bu_3SnH either at high or low concentrations gave **7** as the only observable product.

Registry No.—Tetrachloroethylene, 127-18-4; anthracene, 120-12-7; **1**, 17189-63-8; **3**, 24162-33-2; **4**, 24118-59-0; **5**, 24118-60-3; **2**, 24162-34-3.

Acknowledgment.—We wish to thank the donors of the Petroleum Research Fund administered by the American Chemical Society for support of this work.

(15) S. J. Cristol and N. L. House, *J. Amer. Chem. Soc.*, **74**, 2193 (1952).

Halogenation with Copper(II) Halides. Synthesis of Copper(I) Bromide–Diolefin Complexes

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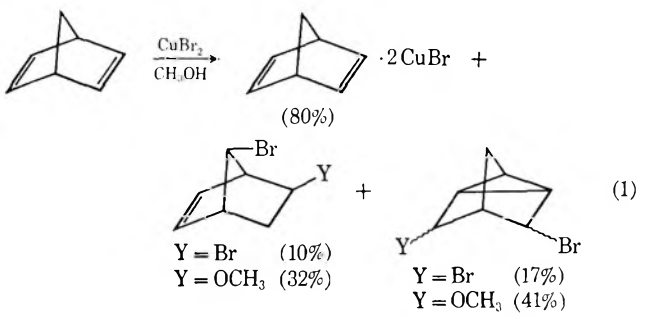
Copper(I) halide–olefin complexes have been prepared by treatment of an ethanolic solution of copper(II) halide and olefin with sulfur dioxide.[1] This technique, which is dependent upon the reduction of copper(II) to copper(I) by sulfur dioxide, has been utilized for the preparation of both copper(I) chloride– and bromide–olefin complexes. The synthesis of two copper(I) bromide–olefin complexes has been described in which the presence of a reducing agent was not required. The addition of norbornadiene[2] or *cis,trans*-cyclodeca-1,5-diene[1c] to a solution of copper(II) bromide dihydrate in ethanol led directly to the formation and precipitation of the corresponding copper(I) bromide complexes. While it was apparent that a redox reac-

(1) (a) H. L. Haight, J. R. Doyle, N. C. Baenziger, and G. F. Richards, *Inorg. Chem.*, **3**, 1301 (1963); (b) J. H. van den Hende and W. C. Baird, Jr., *J. Amer. Chem. Soc.*, **85**, 1009 (1963); (c) J. C. Trebellas, J. R. Olechowski, and H. B. Jonassen, *Inorg. Chem.*, **4**, 1818 (1965).

(2) E. W. Abel, M. A. Bennett, and G. Wilkinson, *J. Chem. Soc.*, 3178 (1959).

tion between copper(II) bromide and olefin was occurring, the nature of the olefin oxidation product was not defined.

A reexamination of these complex forming reactions has revealed that the reaction involved copper(II) bromide bromination of these diolefins to yield dibromo- and bromoalkoxy alkenes. The copper(I) bromide released during the bromination subsequently coordinated with diolefin and separated as the stable copper(I) bromide–diolefin complex. Equation 1 illustrates the reaction utilizing norbornadiene; a similar result was obtained with *cis,cis*-cycloocta-1,5-diene.



(1)

While the ability of copper(II) halides to halogenate carbonyl compounds and polynuclear aromatics had been previously demonstrated,[3] the halogenation of olefinic and acetylenic bonds by these salts has been described only relatively recently.[3,4] These particular reactions involved refluxing methanolic solutions of copper(II) bromide and unsaturates for 3–100 hr; yields of brominated products ranged from 8 to 100%. A kinetic analysis of the copper(II) bromide bromination of allyl alcohol indicated that the reaction proceeded through the thermally induced dissociation of copper(II) bromide to molecular bromine (eq 2)[3]. The

$$2CuBr_2 \rightleftharpoons 2CuBr + Br_2 \qquad (2)$$

reaction was driven to completion by the removal of the equilibrium concentration of bromine by the unsaturated substrate.

Since the reactions of norbornadiene and cycloctadiene occurred rapidly at room temperature, it may be argued that in these cases the dissociation of the copper(II) salt (eq 2) is promoted by the removal of copper(I) bromide *via* stable complex formation with olefin. It has been observed, however, that simple monoolefins are also readily brominated *at room temperature* by methanolic copper(II) bromide. Even though the copper(I) halide complexes of these olefins are relatively labile under these conditions,[5] the consumption of both copper(I) bromide and bromine by olefin provides a driving force for the reactions. In any event it is apparent that methanol–copper(II) bromide solutions contain an active brominating agent whose generation is *not dependent upon thermal treatment* and that the influence of copper ion coordination on the reaction is significant.

It is known that the relative stabilities of metal ion oxidation states are sensitive to complexation.[6] While in water the equilibrium of eq 2 would be completely in favor of copper(II),[7] coordinating solvents, or ligands, that tend to stabilize copper(I) relative to copper(II), would shift the equilibrium of eq 2 toward molecular bromine. With transition metals possessing large numbers of d electrons, *e.g.* copper(I), stabilization is favored by those unsaturated ligands capable of π bonding with the metal ion.[6] Consequently, ligands possessing such structural features as C=C, C≡N, C=O, P, etc. would be particularly effective for complexing and stabilizing copper(I) and hence promoting the dissociation of copper(II) halides. Several examples of this complexation–dissociation have been described. Bromine has been isolated from solutions of copper(II) bromide in acetonitrile, a strong ligand for the stabilization of lower valent transition metal salts.[8,9] The free halogen and tribomide ion have been detected spectrophotometrically in solutions of copper(II) bromide in a variety of coordinating organic solvents.[10] Olefins have been converted nearly quantitatively to vicinal dibromoalkanes in a few minutes at 25° by copper (II) bromide in acetonitrile and other complexing solvents.[11] In addition, styrene and butene-2 have reduced solutions of copper(II) chloride in methanol and acetonitrile at 100°.[12]

The ability of coordinated copper(II) halides to function as selective halogenating agents for simple olefinic unsaturation would appear real. The scope of these reactions has been studied; the synthetic utility and mechanistic interpretations of this chemistry will be presented in future papers.

Experimental Section

Nmr spectra were recorded on a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Ir spectra were measured on a Beckman IR-5A and a Beckman IR-20 spectrophotometer. Glpc was carried out on a Perkin-Elmer 154D fractometer. Preparative glpc was performed on a Varian Aerograph Autoprep Model A-700. All reagents were obtained from commercial sources and were used as received.

Reaction of Norbornadiene with Methanolic Copper(II) Bromide.—A solution of 890 mg (4 mmol) of anhydrous copper(II) bromide in 5 ml of methyl alcohol was added with stirring at room temperature to a solution of 920 mg (10 mmol) of norbornadiene in 10 ml of methanol. A white precipitate formed immediately. The precipitate was removed by filtration, and was washed with methanol. The complex was dried over calcium chloride in a norbornadiene atmosphere; the yield of norbornadiene di[copper(I) bromide] was 600 mg (79.5%).

Anal. Calcd for $C_7H_8Cu_2Br_2$: C, 22.18; H, 2.13; Br, 42.17. Found: C, 19.59; H, 2.12; Br, 44.88. The stability of the complex is such that accurate analysis is difficult.[2]

The reaction filtrate was analyzed by glpc on a 2 m × 0.25 in. diethylene glycol succinate column at 140° and 150-ml/min helium flow and was shown to contain the following compounds: 3-bromo-5-methoxynortricyclene (11.0 min from air, 41%); *exo,syn*-5-methoxy-7-bromonorbornene-2 (13.0 min, 32%); 3,5-

(3) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **30**, 587 (1965), and references cited therein.

(4) C. E. Castro, *ibid.*, **26**, 4183 (1961).

(5) For a discussion of the formation constants and heats of formation for various copper(I)–olefin complexes, see J. M. Harvilchuck, D. A. Aikens, and R. C. Murray, Jr. *Inorg. Chem.*, **8**, 539 (1969); see also ref 1b. Copper(II)–olefin complexes have not been described.

(6) H. J. Emeleus and J. S. Anderson, "Modern Aspects of Inorganic Chemistry," Routledge and Kegan Paul Ltd., London, 1960, Chapter 6.

(7) L. Pauling, "College Chemistry," W. H. Freeman and Co., San Francisco, Calif., 1951, p 554.

(8) R. A. Walton, *Quart. Rev.* (London), **19**, 126 (1965).

(9) J. C. Barnes and D. C. Hume, *Inorg. Chem.*, **2**, 444 (1963).

(10) W. Schneider and A. V. Zelewsky, *Helv. Chim. Acta*, **46**, 1848 (1963).

(11) W. C. Baird, Jr. unpublished results.

(12) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 1887 (1963).

dibromonortricyclene (22.0 min, 17%); *exo,syn*-5,7-dibromonorbornene-2 (28.5 min, 10%).[13] The products were identified by comparison of their glpc retention times with those of authentic samples obtained by the addition of bromine to norbornadiene in carbon tetrachloride and in methanol.[14] The composition of the product mixture in the latter solvent was identical with that reported above.

Reaction of Cyclooctadiene-1,5 with Methanolic Copper(II) Bromide.—A solution of 15.0 g (0.067 mol) of copper(II) bromide in 75 ml of methanol was added dropwise at room temperature to a stirred solution of 11.0 g (0.102 mol) of cyclooctadiene-1,5 in 30 ml of methanol over a period of 30 min. A white precipitate appeared after a few minutes. The complex was separated by filtration and was washed with methanol and pentane. The complex was dried over calcium chloride in a cyclooctadiene atmosphere to give 13.3 g (80.5%) of bis[cyclooctadiene-copper(I) bromide].

Anal. Calcd for $(C_8H_{12}CuBr)_2$: C, 38.18; H, 4.81; Br, 32.76. Found: C, 38.26; H, 5.14; Br, 33.70.

The complex is identical in structure with that of the corresponding copper(I) chloride complex.[1b]

The reaction filtrate was poured into 200 ml of water and extracted with *n*-pentane (three 150-ml portions). The pentane extracts were combined and dried over magnesium sulfate; the solvent was removed on a rotary evaporator to give 6.7 g of colorless oil. Analysis by glpc (1 m × 0.25 in. 5% polypropylene glycol, 150°, 110-ml/min helium flow) showed in addition to some unreacted cyclooctadiene the following mixture: 5-bromo-6-methoxycyclooctene (2.2 min, 4.6%); 5,6-dibromocyclooctene (4.4 min, 55.8%); two unidentified compounds at 7.6 min (7.2%) and 9.2 min (32.4%). A 5-g sample of the product was chromatographed over 75 g of acid-washed alumina. Elution with pentane provided a sample of 5,6-dibromocyclooctene of 95% purity (glpc).

Anal. Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51; Br, 59.64. Found: C, 35.87; H, 4.48; Br, 59.54.

The nmr spectrum ($CDCl_3$) had the following pattern: δ 5.68 (m, 2, =CH), 4.67 (m, 2, BrCH), 1.83–3.00 (m, 8, CH_2). Hydrogenation of the olefinic dibromide over 10% palladium on charcoal in ethanol consumed 3 mol of hydrogen/mol of dibromide and yielded cyclooctane; this result indicated that no transannular addition reactions had occurred.

Continued elution of the column with 10% ether–pentane permitted the recovery of the two compounds of long retention time. The nmr spectrum ($CDCl_3$) indicated a mixture of polybrominated cyclooctanes; these materials were not characterized further. The addition of bromine to cyclooctadiene in methanol produced a product mixture similar to that previously described; the composition was 9.8% bromo ether, 31.4% dibromocyclooctene, and 59% polybrominated material.

Reaction of Cyclohexene with Methanolic Copper(II) Bromide.—A solution of 8.2 g (0.1 mol) of cyclohexene and 23.0 g (0.1 mol) of copper(II) bromide was stirred at room temperature for 1 hr. The copper(I) bromide (12.9 g, 90%) was separated by filtration, and the filtrate was poured into 100–150 ml of water. The product was extracted with pentane (three 100-ml portions), and the combined pentane extracts were washed with water and dried over magnesium sulfate. The solvent was removed on a rotary evaporator to give 10.2 g of product. Glpc analysis (2 m × 0.25 in. 20% diethylene glycol succinate, 125°, 200-ml/min helium flow) showed the product to be a mixture of *trans*-1-bromo-2-methoxycyclohexane (4.5 min, 25%) and *trans*-1,2-dibromocyclohexane (9.0 min, 75%). Samples of the individual compounds (>95% pure by glpc) were obtained by preparative glpc (12 ft × 3/8 in. 20% FFAP[15] column, 175°, 120-ml/min helium flow). The *trans*-dibromide was identical with an authentic sample. The bromomethoxycyclohexane (n^{20}D 1.4874; lit. n^{20}D 1.4884[16]), had the following nmr pattern: δ 2.74–4.50 (m, 2, CHO, CHBr), 3.33 (s, 3, CH_3O), 0.75–2.50 (m, 8, CH_2).

Anal. Calcd for $C_7H_{13}BrO$: C, 43.54; H, 6.78; Br, 41.39. Found: C, 43.95; H, 7.00; Br, 41.16.

Registry No.—5,6-Dibromocyclooctene, 24165-06-8.

(13) The isomeric nortricyclene derivatives were not resolved under these glpc conditions. The reported toxicity of these materials discouraged a detailed analysis of the reaction products.

(14) S. Winstein and M. Shatavsky, *Chem. Ind.* (London), 56 (1956).

(15) Varian Aerograph, Walnut Creek, Calif.

(16) S. Winstein and R. B. Henderson, *J. Amer. Chem. Soc.*, **65**, 2196 (1943).

Some Transformations of 1-Methyl-1-dichloromethylcyclohexane Derivatives

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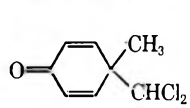
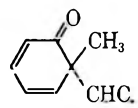
Received December 12, 1969

Recent studies on the chemistry of cyclohexadienones **1**[1] and **2**[2] yielded interesting tangential data which are presented herewith.

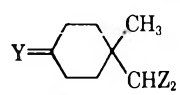


1

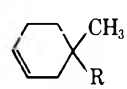


2

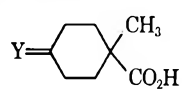
4-Dichloromethyl-4-methylcyclohexanone (**3a**), the product of hydrogenation of **1**, was converted to the dichloride **3b** by Wolff–Kishner reduction of its semicarbazone, to the olefin **4a** by a Bamford–Stevens reduction of its tosylhydrazone, and to the ketal **3c** by treatment with ethylene glycol and acid. Exposure of each of the products to sodium ethylene glycolate in ethylene glycol led to the ethylene acetals **3d**, **4b**, and **3e**, respectively, whose acid hydrolyses gave aldehydes **3f**,[3] **4c**,[4] and **3g**, respectively. Oxidation of these aldehydes yielded acids **5a**,[3] **4d**,[5] and **5b**,[6] respectively.



3a, Y = O; Z = Cl
b, Y = H_2; Z = Cl
c, Y = $(OCH_2)_2$; Z = Cl
d, Y = H_2; Z = $(OCH_2)_2$
e, Y = Z = $(OCH_2)_2$
f, Y = H_2; Z = O
g, Y = Z = O



4a, R = $CHCl_2$
b, R = $CH(OCH_2)_2$
c, R = CHO
d, R = CO_2H



5a, Y = H_2
b, Y = O

The acetylation, a consequence of two consecutive chloride displacements or chlorocarbene formation, alcohol addition, and subsequent chloride displacement, represents a crucial step of an unusual method of construction of quaternary carboxyl functions. While the mechanism of the acetylation was not determined, the first step, proton abstraction, of one of the alternate paths, the carbene route, was shown to be operative. Under the reaction conditions the dichloride **3b** underwent deuterium exchange, whereas its acetal **3b** did not.

As a follow-up of a study of hydrogenation of dienone **2**,[2] hydride reductions of **2** and its hydro derivatives were undertaken. The formation of a single alcohol (**6**) on reduction of the dienone with sodium borohydride in ethanol has been reported already.[2] Hydrogenation

(1) E. Wenkert, F. Haviv, and A. Zeitlin, *J. Amer. Chem. Soc.*, **91**, 2299 (1969).

(2) E. Wenkert, P. Bakuzis, R. J. Baumgarten, D. Doddrell, P. W. Jeffs, C. L. Leicht, R. A. Mueller, and A. Yoshikoshi, *ibid.*, **92**, 1617 (1970).

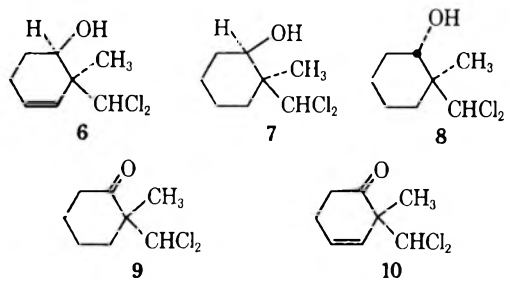
(3) W. Parker and R. A. Raphael, *J. Chem. Soc.*, 1723 (1955).

(4) H. Pines, R. J. Pavlik, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **73**, 5738 (1951).

(5) T. Inukai and M. Kasai, *J. Org. Chem.*, **30**, 3567 (1965), and references cited therein.

(6) M. Rubin and H. Wishinsky, *J. Amer. Chem. Soc.*, **68**, 338 (1946).

of the alcohol afforded a saturated carbinol (**7**) which proved to be the major of two epimeric products of lithium aluminum hydride reduction of the saturated ketone **9**. The stereochemistry of these alcohols, **7** and **8** (and, hence, of **6** also), was assigned as pictorialized on the basis of their ease of elution on column chromatography and the nature of the proton magnetic resonance (pmr) signal of their hydroxymethine functions. On the assumption of the prevalence of cyclohexane chair and equatorial dichloromethyl conformations in deuteriochloroform solutions of the alcohols, the axial hydroxyl group of **7** would be expected to make this cyclohexanol elute more rapidly than its epimer **8** and display a smaller half band width of its hydroxymethine multiplet than **8**. These expectations were in conformity with observation, the spectra revealing half-band widths of *ca.* 7 and 15 cps and hydroxy singlets for alcohols **7** and **8**, respectively.



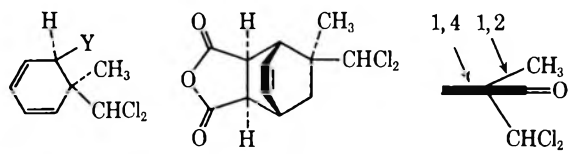
Comparison of the pmr spectra of deuteriochloroform and deuteriopyridine solutions of cyclohexanols **7** and **8** was expected to yield data of value for stereochemical diagnosis.[7] The axial hydroxyl group of **7** is close to the equatorial dichloromethyl group but distant from the methyl substituent, in consonance with a $\Delta\delta$ value (*i.e.*, $\delta_{CDCl_3} - \delta_{C_5D_5N}$ in ppm) of -0.49 for the dichloromethyl moiety and merely -0.01 for the methyl unit, whereas the equatorial hydroxyl group of **8** is proximate to both vicinal substituents, in agreement with -0.53 and -0.12 values, respectively. Since, however, the polar dichloromethyl group itself introduces a solvent shift, $\Delta\delta = -0.37$ for the chlorohydrocarbon **3b**, and since solvent shifts of neighboring substituents probably are not additive, doubt is cast upon the significance of the aforementioned values (Table I).

TABLE I
AROMATIC SOLVENT SHIFTS

Compd	Group	$CDCl_3$	C_5D_5N	C_6D_6
7	Me	1.10	1.11	0.94
	$CHCl_2$	6.01	6.50	6.00
8	Me	1.12	1.24	0.90
	$CHCl_2$	6.03	6.56	5.96
3b	Me	1.11	1.06	0.96
	$CHCl_2$	5.63	6.00	5.24

The striking difference of the effect of benzene ($\Delta\delta$ = 0.39) on the dichloromethine chemical shift of compound **3b** from the effect of pyridine ($\Delta\delta = -0.37$) points to dissimilar solute–solvent interactions of the two aromatic solvents. It probably reflects a difference of orientation of the plane of the aromatic ring to the dipole axis of **3b** in the complex responsible for the solvent-induced shifts. Both solvents would be expected to be proximate to the positive end of the dipole. While, however, the benzene plane should be as nearly perpendicular to the dipole axis as possible, thus placing the hydrogen of the dichloromethyl group into the shielding zone of the aromatic ring,[8] the pyridine plane may lie on the dipole axis and have its nitrogen oriented toward the acidic dichloromethyl hydrogen, thus placing the latter in the deshielding zone of the aromatic nucleus. The minimal effect of benzene on the dichloromethyl groups of compounds **7** and **8**, $\Delta\delta$ = 0.01 and 0.07, respectively, contrasted to that of substance **3b**, may be due to alcohol–benzene hydrogen-bond complexes being present in lieu of or in addition to the dipole complexes.

Lithium aluminum hydride reduction of **2** in ether solution at Dry Ice–acetone bath temperature produced ketone **10** and dienol **11a**, while similar reduction at salt–ice bath temperature led to these products in minor amounts in accompaniment with the diene **11b** in major quantity. Reduction at room temperature in tetrahydrofuran solution gave some diene **11b** and alcohol **6**, but mostly ketone **10**. Reduction of **10** with lithium aluminum hydride afforded alcohol **6** exclusively. Oxidation of the dienol **11a** with manganese dioxide reverted it to the dienone **2**, and hydrogenation transformed it into the saturated alcohol **7** and some ketone **9**. The liquid diene **11b** was characterized as its maleic anhydride adduct **12** whose stereochemistry was determined by analysis of its pmr spectrum and that of its dihydro derivative.



11a, Y = OH
b, Y = H

12

13

The diverse results of the reduction of **2** by lithium aluminum hydride can be explained on the basis of the initial reaction occurring at the site of the carbonyl group and the primary reduction intermediate either surviving, undergoing carbon–oxygen bond scission,[9] or suffering double-bond isomerization and even experiencing further reduction, the last two procedures conceivably taking place during aqueous work-up.[10] The most interesting features of the chemical reductions were the preponderant formation of axial alcohols in the reactions of ketones **2**, **9**, and **10**, and the high stereoselectivity of especially the first and third processes. These observations can be interpreted most readily in terms of the reactant-like transition-state model of Felkin for ketone addition reactions.[11] The following can be offered as rationale for the transformation of ketone **2** into a single cyclohexadienol (**11a**) and for the contrasting liberation of a *ca.* 3:2 mixture of stereo-

(7) (a) A. C. Huitric, J. B. Carr, and W. F. Trager, *J. Pharm. Sci.*, **55**, 211 (1966); (b) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968), and references therein; (c) C. R. Narayanan, N. R. Bhadane, and M. R. Sarma, *Tetrahedron Lett.*, 1561 (1968).

(8) T. Ledaal, *ibid.*, 1683 (1968).

(9) *Cf.* M. P. Cava and K. Narasimhan, *J. Org. Chem.*, **34**, 3641 (1969).

(10) D. I. Schuster, J. M. Palmer, and S. C. Dickerman, *ibid.*, **31**, 4281 (1966); J. A. Marshall, N. H. Anderson, and A. R. Hochstetler, *ibid.*, **32**, 113 (1967).

(11) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); M. Chérest and H. Felkin, *ibid.*, 2205 (1968).

isomeric cyclohexadienols in the hydride reduction of 6-methyl-6-allyl-2,4-cyclohexadienone.[12] The bulky, polar dichloromethyl group of 2 would be expected to assume a quasiaxial stance in order to minimize nonbonded interactions with its neighbors and dipole–dipole repulsions. Hence both steric and electronic factors invite hydride attack on 2 from the methyl side of the nuclear plane (*cf.* **13**). The lack of significant steric or electronic dissimilarity of methyl and allyl groups leads to lowered directional discrimination in the hydride reduction of the cyclohexadienone containing these α-alkyl substituents. The powerful polar effect of the dichloromethyl group is illustrated strikingly in the 1,4 addition reactions of 2 with Grignard reagents. Despite the absence of steric factors, the nucleophile shows preference for the methyl side of the nearly planar substance (*cf.* **13**).[2,13]

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared spectra were obtained on Perkin–Elmer Model 137 and 137B spectrophotometers. Proton magnetic resonance spectra of deuteriochloroform solutions (unless otherwise noted) containing tetramethylsilane (δ 0 ppm) as internal standard were taken on Varian Associates Model A-60 and HA-100 spectrometers. Solvent-shift studies were carried out on 3% solutions.

4-Dichloromethyl-4-methylcyclohexanone (3a).—A mixture of 1.91 g of ketone 1 and 200 mg of 10% palladium–charcoal in 15 ml of ethyl acetate was hydrogenated at atmospheric pressure and room temperature. Upon cessation of hydrogen uptake the catalyst was filtered and the filtrate evaporated. Crystallization of the residual oil from hexane gave 1.90 g of ketone **3a**: mp 44–46°; infrared (Nujol) C=O 5.85 (s) μ; pmr δ 1.40 (s, 3, Me), 5.83 (s, 1, $CHCl_2$).

Anal. Calcd for $C_8H_{12}OCl_2$: C, 49.25; H, 6.20. Found: C, 48.96; H, 5.99.

Its semicarbazone was crystallized from ethanol (mp 191–193°).

Anal. Calcd for $C_9H_{15}ON_3Cl_2$: C, 42.85; H, 5.95; N, 16.64. Found: C, 42.81; H, 6.17; N, 16.65.

Its *p*-toluenesulfonylhydrazone was crystallized from aqueous ethanol (mp 158–160°).

Anal. Calcd for $C_{15}H_{20}O_2N_2SCl_2$: C, 49.58; H, 5.51. Found: C, 49.54; H, 5.79.

4-Dichloromethyl-4-methylcyclohexanone Ethylene Ketal (3c).—A solution of 970 mg of ketone **3a**, a few crystals of *p*-toluenesulfonic acid, and 340 mg of ethylene glycol in 50 ml of benzene was refluxed for 12 hr, while water was being removed azeotropically. Upon addition of sodium bicarbonate the cooled mixture was extracted with ether. The extract was dried over sodium sulfate and evaporated. Crystallization of the solid residue, 850 mg, from hexane yielded ketal **3c**: mp 99–100°; pmr δ 1.15 (s, 3, Me), 3.96 (s, 4, oxymethylenes), 5.72 (s, 1, $CHCl_2$).

Anal. Calcd for $C_{10}H_{16}O_2Cl_2$: C, 50.21; H, 6.69. Found: C, 50.41; H, 6.56.

1-Dichloromethyl-1-methylcyclohexane (3b).—A mixture of 20.5 g of **3a** semicarbazone and 13.0 g of potassium hydroxide in 500 ml of diethylene glycol was refluxed for 4 hr. The cooled mixture was diluted with water and extracted with ether. The extract was dried and evaporated. Filtration of the residual oil through a short alumina column and distillation yielded 11.0 g of liquid **3b**: bp 55° (1.7 Torr); pmr δ 1.11 (s, 3, Me), 5.68 (s, 1, $CHCl_2$).

Anal. Calcd for $C_8H_{14}Cl_2$: C, 53.04; H, 7.74. Found: C, 52.88; H, 7.65.

4-Dichloromethyl-4-methylcyclohexene (4a).—A mixture of 640 mg of **3a** *p*-toluenesulfonylhydrazone and sodium ethylene glycolate, from 1.2 g of sodium, in 15 ml of ethylene glycol was refluxed for 2 hr. The mixture was distilled, taken up in ether, dried, and evaporated. Filtration of the oil through a short alumina column and distillation gave 300 mg of liquid **4a**: bp 45–46° (1.7 Torr); infrared (neat) C=C 6.01 (w) μ; pmr δ 1.12 (s, 3, Me), 1.6–1.8 (m, 2, methylene), 1.9–2.2 (m, 4, allyl H's), 5.6–5.8 (m, 2, olefinic H's), 5.70 (s, 1, $CHCl_2$).

Anal. Calcd for $C_8H_{12}Cl_2$: C, 53.63; H, 6.70. Found: C, 53.93; H, 6.67.

Ethylene Acetals.—A solution of sodium ethylene glycolate, from 1.3 g of sodium, and 540 mg of **3b** in 20 ml of ethylene glycol was refluxed under nitrogen for 20 hr. The cooled mixture was diluted with 200 ml of water and extracted with hexane. The extract was dried, concentrated, filtered through a short alumina column, and evaporated. Purification of the residue by gas chromatography on a Carbowax 20M column gave 320 mg of liquid **3d** [pmr δ 0.90 (s, 3, Me), 1.2–1.7 (m, 10, methylenes), 3.88 (s, 4, oxymethylenes), 4.50 (s, 1, oxymethine)], which was used as such in further experiments.

The same reaction for 48 hr and the same work-up was carried out on 360 mg of **4a**. It produced 150 mg of liquid **4b** [pmr δ 0.92 (s, 3, Me), 1.3–1.7 (m, 2, methylene), 1.7–2.2 (m, 4, allyl H's), 3.89 (s, 4, oxymethylenes), 4.61 (s, 1, oxymethine), 5.6–5.7 (m, 2, olefinic H's)], which was used as such in further experiments.

A similar reaction for 48 hr and a similar work-up was performed on 1.92 g of **3c**. It led to 650 mg of liquid **3e** [pmr δ 0.95 (s, 3, Me), 1.5–1.8 (m, 8, methylenes), 3.89–4.01 (m, 8, oxymethylenes), 4.58 (s, 1, oxymethine)] which was used as such in further experiments.

Aldehydes.—Treatment of acetal **3d** with acid and 2,4-dinitrophenylhydrazine yielded an aldehyde derivative. Crystallization from methanol gave **3f** 2,4-dinitrophenylhydrazone, mp 154–155° (lit.[3] mp 154–155°).

A solution of 80 mg of acetal **4b** in 3 ml of a 50% aqueous dioxane solution of 10% sulfuric acid was kept at room temperature for 12 hr. Sodium bicarbonate was added, and the mixture extracted with chloroform. The extract was dried and evaporated. The residual oily aldehyde, 50 mg, was converted into a derivative. Crystallization from ethanol gave **4c** semicarbazone, mp 170° (lit.[4] mp 170–172°).

Acetal **3e**, 100 mg, was hydrolyzed in the same manner as **4b** and the crude ketoaldehyde **3g** [infrared (CCl_4) aldehyde CH 3.70 (w), C=O 5.80 (s) μ] was used immediately for oxidation to an acid (*vide infra*).

Acids.—A mixture of 100 mg of **3d** and 1 ml of Jones reagent in 2 ml of acetone was stirred at room temperature for 30 min. It was extracted with ether; the extract was dried and evaporated. Sublimation of the residual oil, 70 mg, gave 1-methylcyclohexanecarboxylic acid (**5a**), mp 36–38° (lit.[3] mp 37–38°).

A mixture of 50 mg of aldehyde **4c**, 100 mg of sodium hydroxide, and 80 mg of silver nitrate in 3 ml of dioxane and 7 ml of water was stirred at 0° for 24 hr. The precipitate was filtered, and the filtrate was acidified and extracted with chloroform. The extract was dried and evaporated. Sublimation of the residual oil, 30 mg, gave 1-methyl-3-cyclohexenecarboxylic acid (**4d**): mp 77–79° (lit.[5] mp 78–79°), mmp 78°; infrared spectrum identical with that of an authentic sample.

Crude **3g** was treated with 2 ml of Jones reagent at 0° for 5 min. Work-up as above yielded 35 mg of oil whose sublimation led to 4-carboxy-4-methylcyclohexanone (**5b**): mp 79–81° (lit.[6] mp 78–79°); pmr δ 1.42 (s, 3, Me).

Deuterium Exchange.—The above acetylation of **3b** was carried out in O-deuterated ethylene glycol[14] for 24 hr, and starting material was separated by gas chromatography. Its pmr spectrum revealed all signals characteristic of **3b** except that at 5.68 ppm. A 48-hr "acetalation" of **3d** in O-deuterated ethylene glycol gave **3d** unchanged.

Lithium Aluminum Hydride Reductions.—A mixture of 1.00 g of 2-methyl-2-dichloromethylcyclohexanone (9)[2] and 200 mg of lithium aluminum hydride in 100 ml of ether was stirred at room temperature for 2 hr. Sodium sulfate decahydrate was added and the mixture was shaken thoroughly and filtered. The filtrate was washed with water, dried, and evaporated. Chromatography of the residue on silica gel and elution with benzene yielded 625 mg of an oil whose distillation [bath temperature 80° (0.2 Torr)] and sublimation [45° (0.1 Torr)] gave alcohol **7**: mp 43–44°; infrared (Nujol) OH 2.85 (m) μ; pmr δ 3.85 (m, 1, oxymethine).

(12) H.-J. Hansen, B. Sutter, and H. Schmid, *Helv. Chim. Acta*, **51**, 828 (1968).

(13) *Cf.* D. M. S. Wheeler and M. M. Wheeler, *J. Org. Chem.*, **27**, 3796 (1962), and references therein.

(14) D. J. Cram and B. Rickborn, *J. Amer. Chem. Soc.*, **83**, 2178 (1961).

Anal. Calcd for $C_8H_{14}OCl_2$: C, 48.75; H, 7.16. Found: C, 48.91; H, 7.22.

Continued elution with benzene led to 159 mg whose distillation [bath temperature 80° (0.2 Torr)] gave alcohol **8**: mp 41–42°; infrared (Nujol) OH 2.91 (m) μ, fingerprint region vastly different from that of **7**; pmr δ 3.85 (m, 1, oxymethine).

Anal. Calcd for $C_8H_{14}OCl_2$: C, 48.75; H, 7.16. Found: C, 48.73; H, 7.12.

A mixture of 1.00 g of ketone **10** and 0.38 g of lithium aluminum hydride in 100 ml of ether was stirred at 0° for 1 hr. Work-up as above gave 970 mg of alcohol **6**, mp 61–62°.

A mixture of 270 mg of alcohol **6** and 50 mg of 10% palladium–charcoal in 5 ml of ethanol was hydrogenated at room temperature and atmospheric pressure. Usual work-up yielded 270 mg of alcohol **7**, mp 43–44°.

A solution of 5.00 g of ketone **2** in 10 ml of ether was added over a 1.5-hr period to a suspension of 500 mg of lithium aluminum hydride in 50 ml of ether under nitrogen in a Dry Ice–acetone bath. The mixture was stirred for 3 hr, 3 ml of methyl formate added, and the stirring continued for 30 min. After the mixture was warmed to 0°, 1 ml of water and 1 ml of 10% sodium hydroxide solution were added and the mixture was filtered. The filtrate was washed with 5% sodium bicarbonate solution and with water, dried, and evaporated. Crystallization of the residue from 5 ml of 3:1 hexane–benzene yielded 1.74 g of **10**. Chromatography of the mother liquor on Florisil and elution with petroleum ether gave 0.87 g more of **10**. Elution with 3:1 petroleum ether–benzene led to 1.64 g of a solid whose sublimation [45° (0.1 Torr)] yielded dienol **11a**: mp 57–57.5°; infrared (Nujol) OH 3.01 (s) μ; pmr δ 1.21 (s, 3, Me), 4.09 (m, 1, oxymethine), 5.95–6.15 (m, 4, olefinic H's), 6.23 (s, 1, $CHCl_2$); pmr (pyridine) δ 1.27 (s, 3, Me), 4.20 (m, 1, oxymethine), 5.85–6.10 (m, 4, olefinic H's), 6.64 (s, 1, $CHCl_2$).

Anal. Calcd for $C_8H_{10}OCl_2$: C, 49.76; H, 5.23. Found: C, 49.64; H, 5.24.

A mixture of 88 mg of **11a** and 600 mg of manganese dioxide in 75 ml of ether was stirred at room temperature for 3 hr and then filtered. Evaporation of the filtrate gave 86 mg of the dienone **2**.

A mixture of 70 mg of **11a** and 10 mg of 10% palladium–charcoal in 5 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. After cessation of hydrogen uptake the mixture was filtered and the filtrate evaporated. A benzene solution of the residue was passed through a column of silica gel and evaporated. Pmr analysis of the residual mixture, 64 mg, showed it to consist of 90% alcohol **7** and 10% ketone **9**.

A solution of 13.6 g of ketone **2** in 40 ml of tetrahydrofuran was added over a 10-min period to a suspension of 1.95 g of lithium aluminum hydride in 140 ml of tetrahydrofuran under nitrogen. The mixture was stirred for 0.5 hr, sodium sulfate decahydrate then added, and the mixture filtered. The filtrate was dried and evaporated and the residue chromatographed on Florisil. Elution with petroleum ether yielded 500 mg of liquid diene **11b**: infrared ($CHCl_3$) C=C 6.01 (s), 6.12 (m) μ; pmr δ 1.20 (s, 3, Me), 2.38 (q, 2, J = 18.0, 2.5 cps, methylene), 5.4–6.0 (m, 4, olefinic H's), 5.66 (s, 1, $CHCl_2$). It was characterized as a maleic anhydride adduct (*vide infra*). Elution with 20:1 petroleum ether–ether gave 7.6 g of ketone **10**, while elution with a 4:1 mixture afforded 1.2 g of alcohol **6**.

A solution of 5.00 g of ketone **2** in 10 ml of ether was added over a 30-min period to a suspension of 500 mg of lithium aluminum hydride in 50 ml of ether at *ca.* −5°. The mixture was stirred for 30 min, 1 ml of 10% sodium hydroxide solution added, and the mixture filtered. The filtrate was washed with sodium bicarbonate solution and with water, dried, and evaporated. Distillation [45° (0.5 Torr)] of the residue yielded 1.86 g of a mixture, shown by gas phase chromatography (SE-30 column) to consist of 90% **11b** and 10% **10**. Chromatography of the distillation residue on silica gel and elution with petroleum ether gave 56 mg of diene **11b**. Elution with 1:1 benzene–petroleum ether led successively to 338 mg of **10** and 1.08 g of a complex alcohol mixture whose distillation [75° (0.4 Torr)] afforded 577 mg of a mixture shown by manganese dioxide oxidation (*vide supra*) to contain *ca.* 40% dienol **11a**.

Anhydride 12.—A solution of 340 mg of diene **11b** and 350 mg of maleic anhydride in 1 ml of benzene was refluxed for 48 hr and then evaporated. Chromatography of the residue on Florisil and elution with 4:1 benzene–petroleum ether gave 215 mg of a mixture of Diels–Alder adducts from which 120 mg of **12** could be obtained on crystallization from benzene–petroleum ether. Recrystallization from benzene yielded **12**: mp 146–146.5°; infrared (Nujol) C=O 5.38 (w), 5.46 (w), 5.64 (s) μ; pmr δ 1.37 (s, 3, Me), 1.4–1.7 (m, 2, methylene), 3.0–3.7 (m, 4, methines), 5.42 (s, 1, $CHCl_2$), 6.2–6.5 (m, 2, olefinic H's).

Anal. Calcd for $C_{12}H_{12}O_3Cl_2$: C, 52.38; H, 4.39. Found: C, 52.53; H, 4.31.

Analysis of the pmr spectrum of the first mother liquor showed it to contain predominantly **12** but also some of its isomer epimeric at the methyl-substituted site: pmr δ 1.18 (s, 3, Me), 5.63 (s, 1, $CHCl_2$).

A mixture of 100 mg of **12** and 10 mg of 10% palladium–charcoal in 5 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. The mixture was filtered and the filtrate evaporated. A benzene solution of the residue, 100 mg, was passed through a Florisil column and evaporated. Sublimation [80° (0.1 Torr)] of the residue yielded dihydro-**12**: mp 161–162°; infrared (Nujol) C=O 5.37 (m), 5.63 (s) μ; pmr δ 1.31 (s, 3, Me), 5.82 (s, 1, $CHCl_2$).

Anal. Calcd for $C_{12}H_{14}O_3Cl_2$: C, 52.00; H, 5.09. Found: C, 51.98; H, 5.22.

Registry No.—**3a**, 24463-33-0; semicarbazone of **3a**, 24463-34-1; *p*-toluenesulfonylhydrazone of **3a**, 24463-35-2; **3b**, 24147-13-5; **3c**, 24463-37-4; **3d**, 24463-38-5; **4a**, 24463-39-6; **4b**, 24463-40-9; **5b**, 24463-41-0; **6**, 24463-42-1; **7**, 24463-43-2; **8**, 24463-44-3; **11a**, 24463-45-4; **11b**, 24463-46-5; **12**, 24463-47-6; dihydro-**12**, 24463-48-7.

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Iodonium Salts from Organolithium Reagents with *trans*-Chlorovinyliodoso Dichloride[1,2]

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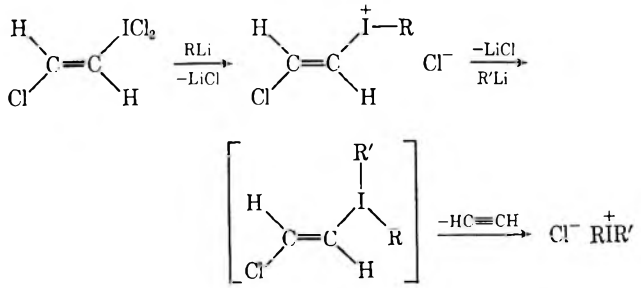
The aim of the present work was to adapt a recently reported synthesis of diaryliodonium salts[3] to the synthesis of iodonium salts having one or two heterocyclic, alkyl, or bicycloalkyl groups, according to the following scheme.



Di-2-thienyliodonium and phenyl-2-thienyliodonium salts, previously obtained by direct electrophilic substitution of thiophene,[4] were prepared in 72 and 38%

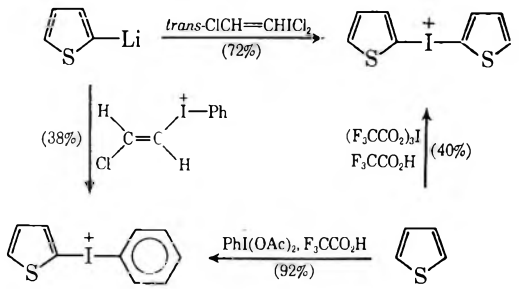
(1) Supported in part by National Science Foundation Grant No. GP-4425 to F. M. B. and by American Chemical Society Petroleum Research Fund Grant No. 231 to R. A. N.

(2) Taken from the dissertation of R. A. Nathan submitted in partial fulfillment of the requirements for the Ph.D. degree, 1969.

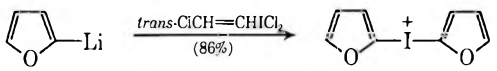
(3) F. M. Beringer and R. A. Nathan, *J. Org. Chem.*, **34**, 685 (1969).

(4) F. M. Beringer, H. E. Bachofner, R. A. Falk, and M. Leff, *J. Amer. Chem. Soc.*, **80**, 4279 (1958).

yields, respectively, by the reaction of 2-thienyllithium with *trans*-chlorovinyliodoso dichloride and phenyl(*trans*-chlorovinyl)iodonium chloride.



By this method it has been possible to prepare for the first time an iodonium salt from furan. The mixed



iodonium chloride–bromide, isolated as soon as the reaction mixture warmed to room temperature, could not be successfully recrystallized, but metathesis to the iodide gave a pure salt. Attempts to prepare phenyl(2-furanyl)iodonium salts from phenyl(2-chlorovinyl)iodonium chloride with 2-furanyllithium were unsuccessful.

Pyridyliodonium salts could not be prepared by the use of 2-pyridyllithium with the iodoso and iodonium reagents. It is not known whether the difficulty lay in an inherent shortcoming of the synthesis or in the instability of 2-pyridyliodonium salts.

In attempts to form iodonium salts with one or two bonds to sp^3 carbon, the same iodoso and iodonium reagents containing the *trans*-chlorovinyl masking group were treated with neopentyllithium and with 1-bicyclo[2.2.1]heptyllithium but gave no iodonium salt. Also, unsuccessful were reactions using vinyllithium, 1-cyclohexenyllithium, 1-perfluoroheptyllithium, and 3,3,3-trifluoropropynyllithium; the causes of these failures are not known.

Experimental Section

Analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Gas chromatography was done on 6-ft columns, packed with 20% SE-30 on Chromosorb W (DMCS-treated), with an Aerograph 1520-A gas chromatograph. Melting points[5] were taken in capillary tubes on a Thomas–Hoover apparatus and corrected.

Neopentyllithium.—Since the low-temperature (10°) synthesis of neopentyllithium[6,7] could not be repeated, a new procedure at higher temperature[8] was developed. A 250-ml round-bottom three-necked flask equipped with a septum cap, reflux condenser, and pressure-equalizing addition funnel was flushed well with argon, flamed, charged with 8.0 g of lithium dispersion[9] and 80 ml of benzene, and kept under a positive pressure of argon. Neopentyl chloride (21.32 g, 200 mmol) in 40 ml of benzene was placed in the addition funnel. After approximately 20% of the alkyl chloride solution had been added, the temperature was raised slowly to the point of exotherm (usually between 75 and 80°), at which time the heat was removed, and gentle reflux was maintained (about 82°) by regulating the rate of addition of the alkyl halide. After this addition, the mixture was heated overnight under reflux. The cooled reaction mixture was filtered through sintered glass under argon. Titration of aliquots from different runs showed a variation from 60 to 90% in the yield of neopentyllithium. Neopentyl bromide gave much lower yields, about 10%.

Di-2-thienyliodonium Iodide and Di-2-furanyliodonium Iodide.—These reactions were carried out at Dry Ice–acetone temperatures as described[3] for diphenyliodonium iodide, except that they were terminated immediately upon warming to room temperature. Work-up was rapid, and all salts were stored below 0°. **Di-2-thienyliodonium iodide** was obtained in 72% yield, mp 131–136° dec, lit.[4] 135–136°.

Di-2-furanyliodonium iodide was similarly obtained in 86% yield, mp 114–116° dec.[10]

Anal. Calcd for $C_8H_6O_2I_2$: C, 24.77; H, 1.56; I, 65.43. Found: C, 24.92; H, 1.45; I, 65.36.

Phenyl(2-thienyl)iodonium chloride was prepared as described previously for phenyl-1-naphthyliodonium chloride **3**, except that it was worked up immediately upon reaching room temperature, giving 1.6 g (38%), mp 149–150.5° dec, lit.[4] 140–141°.

Attempts to Prepare Alkyliodonium Salts.—The unsuccessful reactions of various alkyl- and perfluoroalkyllithium reagents with *trans*-chlorovinyliodoso dichloride and phenyl(*trans*-chlorovinyl)iodonium chloride were run like the successful preparations of diaryliodonium salts.[3] With these salts neopentyllithium gave no iodonium salt and no neopentyl halides. However, with phenyliodoso dichloride,[11] neopentyllithium gave neopentyl chloride and iodide (trace) along with iodobenzene.

When 1-bicyclo[2.2.1]heptyllithium was alllowed to react with *trans*-chlorovinyliodoso dichloride, while no solid was formed, vpc confirmed the presence of both bridgehead iodide and chloride (ratio of *ca.* 5:1). Presumably, the bridgehead iodide results from nucleophilic addition of the bicycloheptyl group to iodine in the iodoso or iodonium reagent.

Reactions of phenyliodoso dichloride and of phenyl(*trans*-chlorovinyl)iodonium chloride with 1-cyclohexenyllithium were equally unsuccessful. In the latter reaction quenching at low temperature with magnesium bromide etherate, with triphenylboron, and with methanol, in an attempt to help break the chlorovinyliodine bond, was also unsuccessful. In all three cases phenyl(*trans*-chlorovinyl)iodonium chloride was recovered.

Registry No.—*trans*-Chlorovinyliodoso dichloride, 24472-17-1; di-2-furanyliodonium iodide, 24472-18-2.

(5) The technique involved in taking melting points of iodonium salts has been discussed previously: F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausner, and E. Sommer, *J. Amer. Chem. Soc.*, **81**, 342 (1959).

(6) D. E. Applequist and D. F. O'Brien, *ibid.*, **85**, 743 (1963).

(7) H. Gilman, H. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *ibid.*, **71**, 1499 (1949).

(8) H. Gilman, F. W. Moore, and O. Baine, *ibid.*, **63**, 2479 (1941).

(9) A dispersion of lithium containing 0.5% sodium in mineral oil. Due to the nonhomogeneity of the dispersion the exact amount of metal in the reaction mixture was unknown. The amount used, however, was in excess of stoichiometry.

(10) Previously unknown compound.

(11) J. Dehn, Jr., Ph.D. Dissertation, Polytechnic Institute of Brooklyn, 1964.

Reactions of 1,1-Bis(trifluoromethyl)alkenols in Sulfuric Acid

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We have recently had an interest in the preparation of fluorinated monomers, including 1,1,1-trifluoro-2-trifluoromethyl-2,4-pentadiene. At least two attempts to prepare this or similar compounds have appeared in the literature.[1,2] Plakhova and Gambaryan[2] reported the preparation of 1,1,1-trifluoro-2-trifluoromethyl-2,4-pentadiene by the phosphorus pentoxide or sulfuric acid dehydration of 1,1-bis(trifluoromethyl)-1-buten-3-ol, but this work may be in doubt (*vide infra*).

(1) M. H. Kaufman and J. D. Brown, *J. Org. Chem.*, **31**, 3090 (1966).

(2) V. F. Plakhova and N. P. Gambaryan, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **4**, 681 (1962).

This paper presents a ready method for the preparation of 1,1,1-trifluoro-2-trifluoromethyl-2,4-pentadiene (**1**) and also, in poor yield, of 1-chloro-1,1-difluoro-2-trifluoromethyl-2,4-pentadiene (**2**).

Mixtures of the isomeric 1,1-bis(trifluoromethyl)-alken-1-ols are obtained in good yield by either the thermal reaction or the aluminum chloride catalyzed reaction of 1-alkenes with hexafluoroacetone. A similar reaction takes place with chloropentafluoroacetone. With the thermal reaction, only the *cis* and *trans* isomers of the 3-alken-1-ols are obtained, while with the aluminum chloride catalyzed reaction the product mixture contains a preponderance of the 2-alken-1-ol. Typical reactions give mixtures as shown in eq 1 and 2.[3]

Thermal reaction

$$(CF_3)_2C{=}O + RCH_2CH{=}CH_2 \xrightarrow{150^\circ} RCH{=}CH_2C(CF_3)_2OH \quad (1)$$

cis, 23%; *trans*, 77%

$AlCl_3$-catalyzed reaction

$$(CF_3)_2C{=}O + RCH_2CH{=}CH_2 \xrightarrow[-20^\circ]{AlCl_3} RCH{=}CHCH_2C(CF_3)_2OH + RCH_2CH{=}CHC(CF_3)_2OH \quad (2)$$

cis, 8%; *trans*, 34% — *cis*, 0%; *trans*, 58%

With R = H, distillation from sulfuric acid yields **1** or **2**. Compound **2** (X = Cl) is isolated as a mixture of

$$C_3H_5C(CF_3)(CF_2X)OH \xrightarrow[\Delta]{H_2SO_4} CH_2{=}CHCH{=}C(CF_3)(CF_2X) \quad (3)$$

(X = F or Cl)

1, X = F; **2**, X = Cl

cis and *trans* isomers identified by nmr data. With R ≠ H starting material is recovered, decomposition occurs, or the alkenols cyclize to tetrahydrofuran derivatives. Results with several adduct mixtures are shown in Table I.

TABLE I

REACTION OF 1,1-BIS(TRIFLUOROMETHYL)ALKEN-1-OLS IN SULFURIC ACID

$RCH_2CH{=}CHC(CF_3)(CF_2X)OH$ (A)

$RCH{=}CHCH_2C(CF_3)(CF_2X)OH$ (B)

$\xrightarrow{H_2SO_4}$ product

Run	R	X	[A]/[B]	Product, %, RCH=CHCH=C(CF₃)(CF₂X)	THF deriv, C[c]
1	H	F	6/4[a]	59	5
2	CH_3	F	6/4[a]	0	68
3	C_3H_7	F	6/4[a]	0	87
4	C_5H_{11}	F	6/4[a]	0	72
5	H	Cl	6/4[a]	6	0
6	H	F	0/10[b]	61	0
7	CH_3	F	0/10[b]	0	71

[a] Equation 1. [b] Equation 2. [c] Equation 4.

(3) (a) V. A. Pattison, *J. Org. Chem.*, **34**, 3650 (1969); (b) N. P. Gambaryan, El. M. Rokhlina, and Yu. V. Zeifman, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **8**, 1425 (1965); (c) H. R. Davis, Abstracts, 140th National Meeting of the American Chemical Society, Sept 1961, Chicago, Ill., Paper No. 53, 25 M.; (d) I. L. Knunyants and B. L. Dyatkin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **2**, 329 (1962).

$$\overset{+}{R}CHCH_2CH_2C(CF_3)(CF_2X)OH \longrightarrow \underset{C}{\text{(H, CF}_3\text{, R, O, CF}_2\text{X ring)}} \quad (4)$$

The tetrahydrofuran derivative is obtained in all cases except with the propylene adduct (R = H) which affords butadiene derivatives (eq 3). In the case where R is H, the unfavorability of a primary carbonium ion minimizes this reaction path and permits oxygen protonation and dehydration of the butadiene to predominate.

With the facile preparation of **1** we have made a cursory examination of a few reactions to determine reactivity and to serve as a chemical structure proof to supplement physical methods.

Polymerization

$$\mathbf{1} \xrightarrow{\text{peroxide}} -(CH_2CH)_xCH{=}C(CF_3)_2$$

Hydrogenation

$$\mathbf{1} \xrightarrow{H_2 \cdot Pd\text{-}C} CH_3CH_2CH_2CH(CF_3)_2$$

Reaction with *n*-butyllithium

$$\mathbf{1} \xrightarrow{C_4H_9Li} \underset{\text{(CF}_3\text{, CF}_2\text{=C, H, C=C, H, CH}_2\text{C}_4\text{H}_9\text{)}}{}$$

Details may be found in the Experimental Section. Structures have been proven by elemental analysis and by infrared and nmr spectroscopy.

As mentioned earlier, Plakhova and Gambaryan[2] reported the preparation of **1** by a several-step synthesis. They give elemental analyses, a boiling point of 65°, and an indication that polymerization could not be effected under a variety of conditions. No further proof of structure is offered except for the method of synthesis. Our findings are that **1** boils at 70–72°, but, more importantly, the high-molecular-weight polymer is obtained readily using standard techniques. In view of these discrepancies we have attempted to repeat their preparation.

Triphenylphosphineacetylmethylene was prepared and allowed to react with hexafluoroacetone to give a good yield of 4,4-bis(trifluoromethyl)-3-buten-2-one (**3**).[2,4] Compound **3** is reportedly reduced to 4,4-bis-(trifluoromethyl)-3-buten-2-ol (**4**) using lithium aluminum hydride (0.50 mol, inverse addition) and isolated as an ether azeotrope (bp 125°). On repeating this reaction as closely as possible we obtained only 5,5-difluoro-4-trifluoromethyl-4-penten-2-ol (**5**), bp 124–126°. When a stoichiometric amount of lithium

$$\underset{\mathbf{3}}{(CF_3)_2C{=}CHC(=O)CH_3} \xrightarrow{0.50\ LiAlH_4} \underset{\mathbf{5}}{CF_2{=}C(CF_3)CH_2CHOHCH_3} \quad (67\%)$$

aluminum hydride was used, the following product mixture resulted.

$$\mathbf{3} \xrightarrow[(33\%)]{0.25\ LiAlH_4} \mathbf{3} + \underset{\mathbf{4}\ (12\%)}{(CF_3)_2C{=}CHCHOHCH_3} + \underset{(21\%)}{\mathbf{5}}$$

(4) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

These data suggest that reduction of **4** to **5** is competitive with reduction of **3** to **4**. It is difficult to rationalize the reported yields of **4** using 0.5 mol of lithium aluminum hydride.

Dehydration of the ether azeotrope from reduction of **3** is the reported final step in the preparation of **1**. We have attempted the sulfuric acid dehydration of **5**, which we obtained under the reported reduction conditions, to determine if a product corresponding to the reported 1,1,1-trifluoro-2-trifluoromethyl-2,4-pentadiene would obtain. There was only extensive degradation. In our hands the reaction sequence does not lead to the reported compounds, and we can neither confirm the work nor suggest alternative products.

Experimental Section[5]

I. Preparation of 1,1-Bis(trihalomethyl)alken-1-ols. $AlCl_3$-Catalyzed Reaction of 1-Alkenes and Hexahaloacetone.—The procedure for the preparation of the alkene–hexahaloacetone adducts is already described for the reaction between hexafluoroacetone and propylene[3] and consists of allowing a cold (−30°) mixture of 2 mol of propylene, 1 mol of hexafluoroacetone, and a catalytic amount of $AlCl_3$ in 1 l. of pentane to warm slowly to 0° and then stirring for 2 hr.

The reagents used are given as follows in the order yield, boiling point, and product composition.

Propylene and hexafluoroacetone: 72%; 97–100°; 60% 1,1-bis(trifluoromethyl)-2-buten-1-ol, 3% *cis*-1,1-bis(trifluoromethyl)-3-buten-1-ol, and 37% *trans*-1,1-bis(trifluoromethyl)-3-buten-1-ol.[3a]

1-Butene and hexafluoroacetone: 79%; 114–117°; 59% *trans*-1;1-bis(trifluoromethyl)2-penten-1-ol, 8% *cis*-1,1-bis(trifluoromethyl)-3-penten-1-ol, and 33% *trans*-1,1-bis(trifluoromethyl)-3-penten-1-ol.[3a]

Propylene and chloropentafluoroacetone: 82%; 127–130°; 50% 1-trifluoromethyl-1-chlorodifluoromethyl-2-buten-1-ol, 40% *trans*-1-trifluoromethyl-1-chlorodifluoromethyl-3-buten-1-ol, and 10% *cis*-1-trifluoromethyl-1-chlorodifluoromethyl-3-buten-1-ol.[7] *Anal.* (for mixture). Calcd for $C_6H_5ClF_5O$: C, 32.53; H, 2.69. Found: C, 32.08; H, 2.73.

1-Hexene and hexafluoroacetone: 79%; 150–153°; 50% *trans*-1,2-bis(trifluoromethyl)-2-hepten-1-ol, 10% *cis*-1,1-bis(trifluoromethyl)-3-hepten-1-ol, and 40% *trans*-1,1-bis(trifluoromethyl)-3-hepten-1-ol.[7] *Anal.* (for mixture). Calcd for $C_9H_{12}F_6O$: C, 43.21; H, 4.72. Found: C, 43.24; H, 4.91.

1-Octene and hexafluoroacetone: 64%; 119–124° (70 mm); 60% *trans*-1,1-bis(trifluoromethyl)-2-nonen-1-ol, 10% *cis*-1,1-bis(trifluoromethyl)-3-nonen-1-ol, and 30% *trans*-1,1-bis(trifluoromethyl)-3-nonen-1-ol.[8] *Anal.* (for mixture). Calcd for $C_{11}H_{16}F_6O$ (mixture): C, 47.49; H, 5.78. Found: C, 47.60; H, 5.68.

II. The Thermal Reaction.—The reaction was carried out as shown in the literature[3] by heating equimolar amounts of olefin and hexafluoroacetone in a sealed tube at 150° for 16 hr.

Reagents used are given as follows in the order, yield, boiling point, and product composition.

Propylene and hexafluoroacetone: 82%; 94–95°; 100% 1,1-bis(trifluoromethyl)-3-buten-1-ol (lit.[3d] 97–98°).

1-Butene and hexafluoroacetone: 74%; 117–119°; 20% *cis*-1,1-bis(trifluoromethyl)-3-penten-1-ol and 80% *trans*-1,1-bis(trifluoromethyl)-3-penten-1-ol.[3a]

III. Reactions of 1,1-Bis(trihalomethyl)alken-1-ols in Sulfuric Acid. 1,1-Bis(trihalomethyl)alken-1-ols from the $AlCl_3$-Catalyzed Reaction of 1-Alkenes and Hexahaloacetone (~60% 2-Alken-1-ol and 40% 3-Alken-1-ol).—The procedure is, in general, similar to that with the 1,1-bis(trifluoromethyl)buten-1-ols below and consists of dissolving the alcohol in sulfuric acid and heating at *ca.* 100° while distilling product (under vacuum if needed).

1,1-Bis(trifluoromethyl)buten-1-ols.—The mixture of isomeric alcohols prepared (above) by the aluminum chloride catalyzed reaction of propylene and hexafluoroacetone (272 g, 1.3 mol) was dissolved in 400 ml of sulfuric acid and heated at 100–110°; 150 g (59%) of essentially pure 1,1,1-trifluoro-1-trifluoromethyl-2,4-pentadiene was distilled (bp 70–72°). The infrared spectrum shows vinyl CH (3100), C=CH_2 (1630), and C=$C(CF_3)_2$ (1660 cm^{-1}), while aliphatic CH absorption is absent (2800–3000 cm^{-1}). The ^1H nmr spectrum shows only vinyl protons as complex groups at 6.5–7.1 ppm (area = 2), 5.6 (1), and 5.9 (1). The ^{19}F spectrum shows a pair of quartets at −14.5 and −20.6 ppm (J = 7 Hz). *Anal.* Calcd for $C_6H_4F_6$: C, 38.34; H, 2.35; F, 60.12. Found: C, 38.11; H, 2.26; F, 59.97.

The pot temperature was then raised to 220° yielding a product which on redistillation afforded 15 g (5%) of 1,1-bis(trifluoromethyl)tetrahydrofuran (bp 106–107°). The infrared spectrum is consistent, showing no OH, vinyl CH, C=C absorption. The ^1H nmr spectrum shows two protons at 4.10 ppm (triplet, J = 6 Hz) and four protons as a complex multiplet at 2.0–2.5 ppm, while the ^{19}F spectrum shows a single peak at −0.2 ppm. *Anal.* Calcd for $C_6H_6F_6O$: C, 34.87; H, 3.03; F, 54.77. Found: C, 34.62; H, 2.91; F, 54.76.

1-Trifluoromethyl-1-chlorodifluoromethylbuten-1-ols.—A mixture of the isomeric alcohols prepared (above) by the aluminum chloride catalyzed reaction of propylene and chloropentafluoroacetone (22.4 g, 0.10 mol) was dissolved in 90 g of sulfuric acid and heated at 100° (50 mm) yielding a dark oil which on washing with water and redistilling afforded 1.2 g (6%) of 1-chloro-1,1-difluoro-2-trifluoromethyl-2,4-pentadiene (bp 101–102°). The infrared spectrum shows vinyl CH (3000–3100), C=CH_2 (1600), and C=$C(CF_3)(CF_2Cl)$ (1660 cm^{-1}). The proton nmr spectrum shows vinyl hydrogens as three complex groups at 6.9 ppm (area = 2), 5.8 (1), and 5.9 (1). The ^{19}F nmr spectrum shows that the product is an equimolar mixture of *cis* and *trans* isomers. The *trans*-1-chloro-1,1-difluoro-2-trifluoromethyl-2,4-pentadiene shows a trifluoromethyl group at −14.6 ppm as a pure triplet (J = 7 Hz) and a CF_2Cl- group at −37.7 ppm as a quartet (J = 7 Hz) split slightly (*ca.* 1 Hz by the *trans* vinyl proton[9]). The *cis* isomer shows the trifluoromethyl group at −20.7 ppm [triplet (J = 7 Hz) of doublets (J = 1 Hz)]. The CF_2Cl- appears as a pure quartet (J = 7 Hz) centered at −26.5 ppm. *Anal.* Calcd for $C_6H_4ClF_5$: C, 35.00; H, 1.94. Found: C, 34.97; H, 2.10.

IV. 1,1-Bis(trifluoromethyl)penten-1-ols, -hepten-1-ols, and -nonen-1-ols.—The reactions of these materials were carried out in the same manner as with the buten-1-ols above. The starting material used are given as follows in the order product, yield, boiling point, and spectroscopic data.

1,1-Bis(trifluoromethyl)penten-1-ols: 1,1-bis(trifluoromethyl)-4-methyltetrahydrofuran, 68%, bp 115–117°, $n^{25}D$ 1.3340. The nmr and infrared spectra are identical with those of the previously authenticated material.[3a]

1,1-Bis(trifluoromethyl)hepten-1-ols: 1,1-bis(trifluoromethyl)-4-propyltetrahydrofuran, 87%, bp 67% (30 mm). The infrared and nmr spectra are consistent with the latter described as follows: HCO, 4.2 (complex); $-(CH_2)_2-$ 1.2–2.5 (complex); CH_3-, 0.91 ppm (triplet, J = 7 Hz). *Anal.* Calcd for $C_9H_{12}F_6O$: C, 43.26; H, 4.81; F, 45.57. Found: C, 43.24; H, 4.83; F, 45.74.

(5) All boiling and melting points are uncorrected. Infrared spectra were obtained as films or Nujol smears using a Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were obtained using a Varian Associates Model HA-100 spectrometer using chloroform as solvent and TMS as internal standard. For fluorine spectra trifluoroacetic acid was used as an external standard. Spectra were run using field frequency lock at 94.1 MHz using a modification described by Douglas.[6] Spectra at both frequencies are accurate to ±0.02 ppm. Glpc work was done on an F & M Model 720 gas chromatograph using a 9-ft column filled with a 20% Carbowax 20M on Chromosorb P packing. Molecular weights were determined by one of two methods depending on the magnitude of the value. For polymer in the range of 5000 ($\bar{M}_n$) the Mechrolab membrane osmometer, Model 501, was employed. Values greater than 50,000 were determined with a Mechrolab vapor pressure osmometer. Elemental analyses were performed by Huffman Laboratories Inc., Wheatridge, Col.

(6) A. W. Douglas, Abstracts of papers presented at the 7th Experimental Nmr Conference, Pittsburgh, Pa., Feb 1966.

(7) The product composition is based on the glpc scan which shows three peaks in the ratios shown and by analogy with the product mixture from propylene and hexafluoroacetone or 1-butene and hexafluoroacetone for which the exact compositions have been determined.[3a]

(8) The product composition is based on the ^{19}F nmr scan which shows three peaks in the ratio shown at −1.8, −1.6, and −0.8 ppm. Assignments are based on the analogy to the products from the reaction of 1-butene and hexafluoroacetone for which the exact composition has been determined.[3a]

(9) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Spectroscopy," Vol. II, Pergamon Press Inc., Elmsford, N. Y., 1966, p 913.

1,1-Bis(trifluoromethyl)nonen-1-ols: 1,1-bis(trifluoromethyl)-4-pentyltetrahydrofuran, 72%, bp, 184°. The infrared and nmr spectra are consistent with the latter described as follows: HCO, 4.2 (complex); $-(CH_2)_2-$, 1.2–2.4 (complex); CH_3- 0.89 ppm (triplet, J = 7 Hz). *Anal.* Calcd for $C_{11}H_{16}F_6O$: C, 47.48; H, 5.79. Found: C, 47.83; H, 5.56.

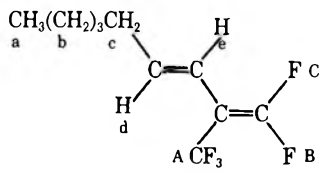
V. 1,1-Bis(trifluoromethyl)-3-alken-1-ols from the Thermal Reaction of 1-Alkenes and Hexafluoroacetone.—Reactions were carried out in a manner identical with those above. The 1,1-bis(trifluoromethyl)-3-buten-1-ols gave a 61% yield of 1,1,1-trifluoro-2-trifluoromethyl-2,4-pentadiene while the 1,1-bis(trifluoromethyl)-3-penten-1-ols yielded 71% 1,1-bis(trifluoromethyl)-4-methyltetrahydrofuran.

VI. Reactions of 1,1,1-Trifluoro-2-trifluoromethyl-2,4-pentadiene (1). Polymerization. In Bulk.—A mixture of 1.90 g (0.10 mol) of 1 and 0.010 g of benzoyl peroxide was placed in a vial, flushed with nitrogen, and heated at 60° for 66 hr. After distilling excess monomer *in vacuo* the residue (0.5 g, 25%) had a molecular weight of 4500. The infrared spectrum shows aliphatic CH (2800–3000), vinyl CH (3000–3100), and $C{=}C(CF_3)_2$ (1680 cm^{-1}). These characteristics and the absence of other C=C absorption indicate that polymerization occurs to a large extent across the less substituted double bond by 1,2 addition.

In Emulsion.—A mixture of 11.8 g (0.06 mol) of 1, 34 ml of water, 0.060 g of potassium persulfate, and 0.36 g of Duponol (surfactant) was placed in a vial, flushed with nitrogen, and heated at 50–60° with vigorous stirring for 20 hr. Evaporation of the water yielded 7.9 g (67%) of a clear, tough polymer having a molecular weight of 83,000. The infrared spectrum is similar to that of the polymer from the bulk reaction.

VII. Hydrogenation.—Diene 1 (48 g), 50 ml of acetic acid, and 0.5 g of 5% Pd-C were placed in a Parr apparatus and hydrogenated at 50 psig. The theoretical amount of hydrogen was quickly absorbed. Filtration and distillation of the product solution yielded 37 g (77%) of 1,1-bis(trifluoromethyl)butane (bp 66–67°). The ^1H nmr spectrum shows three complex envelopes at 0.7–1.4 ppm (area = 3), 1.4–2.2 (4), and 2.6–3.2 (1). The ^{19}F spectrum shows a doublet at −9.88 ppm (J = 7 Hz). *Anal.* Calcd for $C_6H_8F_6$: C, 37.12; H, 4.15. Found: C, 37.47; H, 3.90.

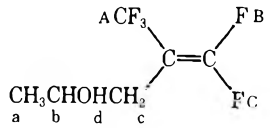
VIII. Reaction with *n*-Butyllithium.—A solution (1.6 *M*, 19 ml) of *n*-butyllithium in hexane (0.030 mol) was added slowly to a cold (0°) solution of 5.7 g (0.030 mol) of 1 in hexane. After stirring for 1 hr, the reaction was hydrolyzed with 5% hydrochloric acid, and after drying over sodium sulfate the organic layer was distilled (8-in. Vigreux) to yield 3.10 g (45%) of *trans*-1,1-difluoro-2-trifluoromethyl-1,3-nonadiene, bp 148–150°. The infrared spectrum is consistent, showing bands at 1630 (-CH=CH-) and 1710 cm^{-1} ($C{=}CF_2$). The nmr spectra are described below.



^1H (δ, ppm): a, 0.90; b, 1.3 (complex); c, 2.0–2.3 (complex); d, 5.8–6.2 (complex); e, 5.70 (doublet, J_{de} = 16 Hz). ^{19}F (ϕ, ppm): A, −17.88 (two doublets, J_{CA} = 28 Hz, J_{BA} = 10 Hz); B, +1.1 (two quartets, J_{AB} = 10 Hz, J_{CB} = 10 Hz); C, −0.3, (two quartets, J_{AC} = 28 Hz, J_{BC} = 10 Hz). *Anal.* Calcd for $C_{10}H_{12}F_6C$: C, 52.67; H, 5.81. Found: C, 52.70; H, 5.91.

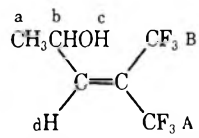
4,4-Bis(trifluoromethyl)-3-buten-2-one.—Triphenylphosphineacetymethylene, mp 201–203° (lit.[4] 205–206°), was prepared according to the method of Ramirez and Dershowitz[4] and allowed to react with a slight excess of hexafluoroacetone as outlined by Plakhova and Gambaryan.[2] The yield of 4,4-bis(trifluoromethyl)-3-buten-2-one was 90%, bp 109–111° [lit.[2] bp 68° (135 mm)]. The infrared spectrum shows C=O (1720) and C=C (1670 cm^{-1}). The ^1H nmr spectrum shows sharp singlets for the vinyl proton (6.97 ppm) and the three methyl protons (2.38 ppm).

IX. Lithium Aluminum Hydride Reduction of 4,4-Bis(trifluoromethyl)-3-buten-2-one. Using 0.50 Mol of $LiAlH_4$.—A solution of 10.3 g (0.050 mol) of 4,4-bis(trifluoromethyl)-3-buten-2-one in 50 ml of ether was cooled to 0° and 0.95 g (0.025 mol) of finely crushed $LiAlH_4$ was added over a period of 1 hr. The reaction mixture was stirred at 0° for 1 hr and after hydrolysis with 5% hydrochloric acid and drying over sodium sulfate, the solvent was removed from the product by careful distillation. The residue was distilled to yield 6.3 g (67%) of 5,5-difluoro-4-trifluoromethyl-4-penten-2-ol. The infrared spectrum shows OH absorption (3500 cm^{-1}) and also $C{=}CF_2$ (1740 cm^{-1}). The nmr spectra are described below.



^1H (δ, ppm): a, 1.25 (doublet, J_{ba} = 6 Hz); b, 3.95 (complex); c, 2.3 (complex); d, 2.30. ^{19}F (ϕ, ppm): A, −17.84 (two doublets, J_{BA} = 10 Hz, J_{CA} = 20 Hz); B, −2.28 (broad multiplet); C, +0.18 (broad multiplet). *Anal.* Calcd for $C_6H_7F_5O$: C, 37.91; H, 3.60. Found: C, 37.77; H, 3.69.

Using 0.25 Mol of $LiAlH_4$.—The reduction was carried out as above using 0.475 g (0.0125 mol) of lithium aluminum hydride. Distillation gave 6.5 g of product, bp 118–134°. Glpc analysis (8-ft silicone grease column) showed the product yield to be starting material, 33%; 5,5-difluoro-4-trifluoromethyl-4-penten-2-ol, 21%; 4,4-bis(trifluoromethyl)-3-buten-2-ol, 12%. The first two materials were identified by comparison of the glpc retention times and infrared spectra with those of the respective authentic compounds. A sample of the third was obtained by preparative scale glpc techniques. The infrared spectrum is consistent, showing OH (3500 cm^{-1}) and $C{=}C(CF_3)_2$ (1680 cm^{-1}) absorptions. The nmr spectra are described below.



^1H (δ, ppm): a, 1.38 (doublet, J_{ba} = 7 Hz); b, 4.9 (complex); c, 2.02 (singlet); d, 6.70 (doublet, J_{bd} = 9 Hz). ^{19}F (ϕ, ppm): A, −13.2 (quartet, J_{BA} = 7 Hz); B, −20.0 (quartet, J_{AB} = 7 Hz). *Anal.* Calcd for $C_6H_6F_6O$: C, 34.62; H, 2.90. Found: C, 34.81; H, 2.85.

Registry No.—**1**, 1422-33-9; *cis*-**2**, 24010-42-2; *trans*-**2**, 24010-43-3; 1,1-bis(trifluoromethyl)tetrahydrofuran, 24010-61-5; 1,1-bis(trifluoromethyl)-4-propyltetrahydrofuran, 24010-62-6; 1,1-bis(trifluoromethyl)-4-pentyltetrahydrofuran, 24010-63-7; 1,1-bis(trifluoromethyl)butane, 24010-64-8; *trans*,1,1-difluoro-2-trifluoromethyl-1,3-monadiene, 24010-44-4; 4,5-difluoro-4-trifluoromethyl-4-penten-2-ol, 24010-65-9; 4,4-bis(trifluoromethyl)-3-buten-2-ol, 656-80-4.

α,α'-Dianilinostilbenes. The Cyanide Ion Catalyzed Dimerization of Aromatic Schiff Bases

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The alkali cyanide catalyzed dimerization of benzaldehyde anil (**1a**) in liquid ammonia has been described to give a fluorescent, yellow dimer to which the anilinoanil structure **2a** was assigned because of the analogous formation of benzoin from benzaldehyde.[1] Since the dimerization product was found to be readily oxidized upon exposure to air to give benzil dianil (**4a**), structure **2a** was suggested to be in equilibrium

(1) H. H. Strain, *J. Amer. Chem. Soc.*, **50**, 2218 (1928).

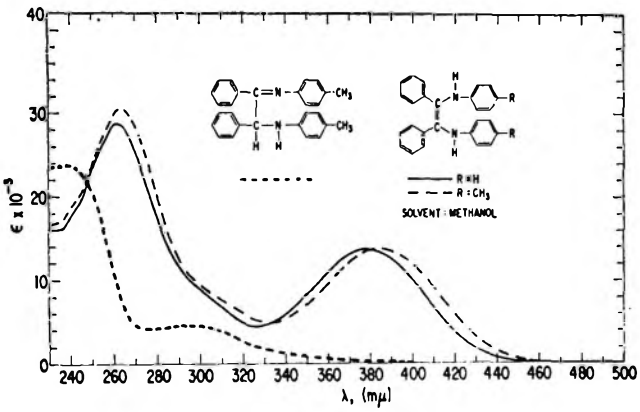
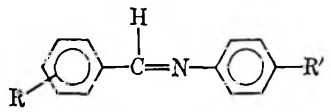
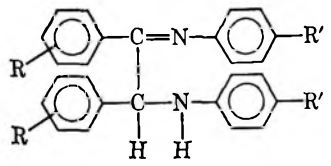


Figure 1.

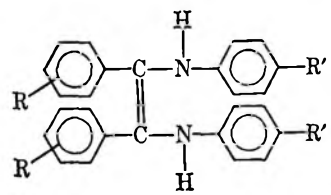
with the enediamine structure **3a**.[2,3] According to a recent communication, however, the reaction of **1a** with an equimolar amount of sodium cyanide in dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) leads directly to benzil dianil.[4]



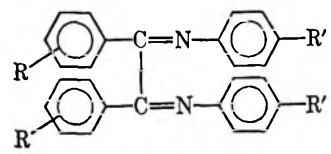
1a–e



2a–e

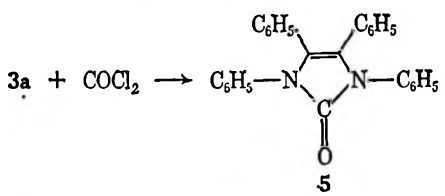


3a–e



4a–e

a, R = H; R′ = H
b, R = 4-CH_3; R′ = H
c, R = 4-OCH_3; R′ = H
d, R = 3,4-OCH_2O–; R′ = H
e, R = H; R′ = CH_3



5

We were prompted to investigate the cyanide ion catalyzed dimerization of **1a** when we needed spectroscopic data of the anilinoanil **2a** for comparison with those of an anilinoanil obtained in the base catalyzed reaction of **1a** with DMSO.[5] This report deals with our findings which differ from those published previously by other authors.

Following the literature procedure for the cyanide ion catalyzed dimerization of **1a** in liquid ammonia,[6] the previously described yellow crystalline dimer with green fluorescence was obtained in 30% yield. We found in the course of this study that the same compound is obtained more conveniently and in higher yield (80%) by treatment of **1a** with a catalytic amount of sodium cyanide in DMF at room temperature, under nitrogen. Likewise, treatment of **1a** with an equimolar quantity of sodium cyanide in DMSO leads to this dimerization product, provided the reaction is carried out in the absence of oxygen. In accordance with earlier[2,3] observations, the dimerization product in solution upon exposure to air is readily oxidized to give benzil dianil (**4a**) in high yield. Thus, the recently observed formation of **4a** in the cyanide ion catalyzed reaction of **1a** does not proceed according to the proposed[4] mechanism but is the result of an inadvertent autoxidation of the previously[1,2] described compound whose mass spectrum we found to be in agreement with the molecular composition $C_{26}H_{22}N_2$.

Spectroscopic data do not, however, support the structure of the dimer, (anilinoanil **2a**). The uv spectrum (Figure 1) shows a longest wavelength absorption maximum at 378 mμ (ε 13,600), quite different from that of benzaldehyde anil.[8] The ir spectrum shows absorption bands in the NH region (see Experimental Section) but no absorption in the region typical of a C=N bond. The nmr spectrum (see Experimental Section) reveals the presence of two magnetically equivalent protons which can be exchanged for deuterium by treatment with D_2O. These data are in excellent agreement with α,α′-dianilinostilbene (**3a**). Whether or not the cyanide ion catalyzed dimerization of **1a** leads to a pure geometrical isomer (either *cis* or *trans*) or to a mixture of isomers has not been investigated. The reaction of the dimerization product with phosgene gives in good yield 1,3,4,5-tetraphenylimidazolone-2 (**5**); however, it is conceivable that a *cis–trans* isomerization occurs under the conditions of phosgenation of **3a**.

Using DMF as a solvent, the cyanide ion catalyzed reaction of anils **1b–1d** was found to give the correspondingly substituted fluorescent α,α′-dianilinostilbenes **3b–3d** in good to excellent yields (see Table I, Experimental Section). Their structure is supported by ir, nmr, and uv spectroscopic data. As observed for the parent compound **3a**, α,α′-dianilinostilbenes **3b–3d** in solution upon exposure to air are readily oxidized to give the corresponding dianils **4b–4d** in excellent yield.

The cyanide ion catalyzed dimerization of benzylidene-*p*-toluidine (**1e**) in DMF leads to a fluorescent yellow crystalline dimer for which spectroscopic data [ir, nmr, uv (see Figure 1)] are in agreement with α,α′-

(2) H. H. Strain, *J. Amer. Chem. Soc.*, **51**, 269 (1929).
(3) P. L. Julian, E. W. Meyer, A. Magnani, and W. Cole, *ibid.*, **67**, 1203 (1945).
(4) J. S. Walia, J. Singh, M. S. Chattha, and M. Satyanarayana, *Tetrahedron Lett.*, 195 (1969).
(5) H.-D. Becker, *J. Org. Chem.*, **34**, 4162 (1969).
(6) An earlier[7] attempt to repeat this dimerization had failed because we did not realize that the reaction should be carried out in a sealed tube.
(7) H.-D. Becker, *ibid.*, **29**, 2891 (1964); *cf.* ref 5.
(8) H. B. Bürgi and J. D. Dunitz, *Chem. Commun.*, 472 (1969).

TABLE I
ALKALI CYANIDE CATALYZED DIMERIZATION OF AROMATIC ANILS

Run	R	R′	1, mmol	Catalyst, mmol	Solvent, ml	Reaction time, hr	Yield of 3, %
1	H	H	60	NaCN, 2	DMF, 50	2	54
2	H	H	200	NaCN, 2	DMF, 75	17	66
3	H	H	200	NaCN, 5	DMF, 100	24	80
4	H	H	20	NaCN, 20	DMSO, 50	15	69
5	H	H	27	KCN, 20	NH_3, 50	24	30
6	4-CH_3	H	110	NaCN, 4	DMF, 50	14	90
7	4-CH_3	H	27	NaCN, 20	NH_3, 50	24	3
8	3,4-O-CH_2-O	H	33	NaCN, 10	DMF, 50	28	69
9	4-OCH_3	H	20	NaCN, 1	DMF, 15	48	35
10	H	CH_3	10	NaCN, 4	DMF, 50	20	51
11	H	CH_3	14	NaCN, 6	DMF, 100	40	58

di-*p*-toluidinostilbene **3e**. Autoxidation of **3e** leads to the expected substituted dianil **4e** in high yield. By contrast, the cyanide ion catalyzed dimerization of benzylidene *p*-toluidine in liquid ammonia gives a (nonfluorescent) colorless crystalline dimer which had been reported[1] previously. The uv spectrum of this dimer whose molecular composition is confirmed by its mass spectrum, is completely different from that of its fluorescent isomer, but is in agreement with that of the originally[1] proposed anilinoanil structure **2e** (see Figure 1). Nmr spectroscopic evidence for structure **2e** is even more revealing. Using deuteriobenzene as solvent, the nmr spectrum of **2e** exhibits two different methyl groups, whereas that of its isomer **3e** shows two magnetically equivalent methyl groups. Furthermore, the CH group and the NH group in **2e** appear as doublets, due to magnetic coupling (see Experimental Section).

In neutral methanol solution, compound **2e** was found to be stable toward autoxidation. In methanol containing a small amount of hydrochloric acid, however, **2e** does oxidize readily upon exposure to air to give the dianil **4e**. The autoxidation is probably preceded by an acid-catalyzed isomerization of **2e** to give **3e**. When dissolved in DMF containing sodium cyanide, the colorless dimer **2e** smoothly isomerizes to give the yellow fluorescent di-*p*-toluidinostilbene **3e**. Apparently, the cyanide ion catalyzed dimerization of anils proceeds according to a mechanism analogous to that of the benzoin condensation,[9] and the formation of α,α'-dianilinostilbenes is due to a subsequent double-bond isomerization of anilinoanils of structure **2**. There is, however, no nmr spectroscopic indication for the previously assumed equilibrium between anilinoanils and their isomeric dianilinostilbenes.

Experimental Section

Dimethylformamide was distilled *in vacuo* and stored over molecular sieves. The melting points of the α,α'-dianilinostilbenes were determined in sealed capillaries, while those of the dianils were taken on a hot-stage microscope. Ir spectra were taken in KBr. Uv spectra were measured in methanol. The nmr spectra were recorded on a 100-Mc Varian spectrometer, using deuteriochloroform as solvent and tetramethylsilane as internal standard.

α,α'-Dianilinostilbene (3a).—A solution of benzaldehyde anil (36.2 g, 0.2 mol) in dry DMF (100 ml) containing pulverized sodium cyanide (250 mg, 5 mmol) was agitated with a stream of nitrogen. After 24 hr the yellow reaction mixture containing a crystalline yellow precipitate was diluted with 150 ml of methanol and kept under nitrogen for 4 hr in the refrigerator. Filtration gave 29 g (80%) of yellow crystalline product showing strong green fluorescence, mp 205–210°. Recrystallization by dissolving the product under N_2 in a small amount of warm chloroform and addition of methanol did not raise the melting point. Spectra follow: uv λ_{max} 378 mμ (ε 13,600); ir 3365, 3400 cm^{-1} (NH); nmr δ 5.50 (2 NH), 6.40–7.60 (20 aromatic H).

Anal. Calcd for $C_{26}H_{22}N_2$ (362.45): C, 86.16; H, 6.12; N, 7.73. Found: C, 86.31; H, 6.24; N, 7.60.

Dianilinostilbenes **3b–3e** were prepared in the same fashion as described for **3a**. Experimental details are summarized in Table I.

α,α'-Dianilino-4,4′-dimethylstilbene (3b).—Yellow crystals with blue fluorescence were recrystallized by dissolving in chloroform and addition of methanol, mp 165–172°. The nmr spectrum of this product indicates a mixture of isomers. Spectra follow: uv λ_{max} 362 mμ (ε 14,400); ir 3355, 3380, 3410 cm^{-1} (NH); nmr δ 2.22 (CH_3), 2.26 (CH_3), 5.46 (NH), 5.50 (NH), 6.40–7.50 (18 aromatic H).

Anal. Calcd for $C_{28}H_{26}N_2$ (390.50): C, 86.11; H, 6.71; N, 7.17. Found: C, 86.12; H, 6.92; N, 7.09.

α,α'-Dianilino-4,4′-dimethoxystilbene (3c).—Yellow crystals with blue fluorescence were recrystallized by dissolving in chloroform and addition of methanol, mp 160–165°. Spectra follow: uv λ_{max} 368 mμ (ε 18,000); ir 3365, 3400 cm^{-1} (NH); nmr δ 3.53 (2 OCH_3), 5.30 (2 NH), 6.30–7.30 (18 aromatic H).

Anal. Calcd for $C_{28}H_{26}N_2O_2$ (422.55): C, 79.59; H, 6.20; N, 6.63. Found: C, 79.62; H, 6.05; N, 6.73.

α,α'-Dianilino-3,4-methylenedioxy-3′,4′-methylenedioxystilbene (3d).—Pale green crystals with blue-green fluorescence were recrystallized by dissolving in chloroform and addition of methanol, mp 180–186°. Spectra follow: uv λ_{max} 375 mμ (ε 16,800); ir 3400 cm^{-1} (NH); nmr δ 5.50 (2 NH), 5.90 (2 OCH_2O), 6.50–7.30 (16 aromatic H).

Anal. Calcd for $C_{28}H_{22}N_2O_4$ (450.47): C, 74.65; H, 4.92; N, 6.22. Found: C, 74.47; H, 4.76; N, 6.04.

α,α'-Di-*p*-toluidinostilbene (3e).—The yellow crystals with blue green fluorescence were recrystallized by dissolving in acetone and addition of ethanol, mp 172–182°. Spectra follow: uv λ_{max} 385 mμ (ε 13,600); ir 3405 cm^{-1} (NH); nmr δ 2.10 (2 CH_3), 5.50 (2 NH), 6.30–7.60 (18 aromatic H).

Anal. Calcd for $C_{28}H_{26}N_2$ (390.50): C, 86.11; H, 6.71; N, 7.17. Found: C, 85.87; H, 6.75; N, 7.15.

Sodium Cyanide Catalyzed Dimerization of Benzylidene-*p*-toluidine in Liquid Ammonia (2e).—A mixture of benzylidene-*p*-toluidine (5 g) and sodium cyanide (1 g) in liquid ammonia (50 ml) was placed in a sealed tube and was kept at room temperature for 24 hr. Evaporation of ammonia from the reaction mixture left a light yellow oil which was triturated under nitrogen with methanol (50 ml). After 10 min, colorless needle-shaped crystals separated from the solution. They were recrystallized by dissolving in little acetone and precipitation with methanol: yield 1.5 g (30%); mp 126–128° (lit.[1] 122°); ir 3355 (NH), 1642 cm^{-1} (C=N). The nmr spectrum of **2e** in benzene-d_6 was recorded on a Varian T-60 spectrometer: δ 1.93 (s, 1 CH_3), 2.13 (s, 1 CH_3), 5.52 (d, J_{AB} = 5 cps, 1 CH), 6.4 (d, J_{AB} = 5 cps, 1 NH), 6.5–7.5 (18 aromatic H). Upon deuteration, the doublet at 6.4 disappears, and the doublet at 5.52 collapses to give a singlet.

Anal. Calcd for $C_{28}H_{26}N_2$ (390.50): C, 86.11; H, 6.71; N, 7.17. Found: C, 85.94; H, 6.65; N, 7.22.

Isomerization of 2e to give 3e.—A solution of **2e** (100 mg) and sodium cyanide (20 mg) in DMF (10 ml) was kept under nitrogen

(9) A. Lapworth, *J. Chem. Soc.*, **83**, 995 (1903); **85**, 1206 (1904).

for 4 hr. Dilution of the yellow solution with aqueous methanol gave a pale yellow crystalline precipitate (80 mg) with blue fluorescence. Its ir spectrum was superimposable with that of **3e** prepared by cyanide ion catalyzed dimerization of **1e** in DMF.

Benzildianil (4a).—A solution of α,α'-dianilinostilbene (1 g) in a mixture of chloroform (120 ml) and methanol (25 ml) was kept standing in an open beaker at room temperature under the hood. After 12 hr, when all solvent had evaporated the brownish crystalline residue was washed with little methanol and recrystallized from boiling methanol, yield 800 mg (80%), mp 146–148° (lit. 145–147°).

Anal. Calcd for $C_{26}H_{20}N_2$ (360.44): C, 86.63; H, 5.59; N, 7.77. Found: C, 86.49; H, 5.60; N, 7.70.

The oxidation of α,α'-dianilinostilbenes **3b–3e** was carried out in the same manner as described for **3a**.

4,4'-Dimethylbenzildianil (4b).—Yellow crystals, mp 149–150°, yield 90%.

Anal. Calcd for $C_{28}H_{24}N_2$ (388.49): C, 86.56; H, 6.23; N, 7.21. Found: C, 86.61; H, 6.32; N, 7.20.

4,4'-Dimethoxybenzil Dianil (4c).—Yellow crystals, mp 153–154°, yield 75%.

Anal. Calcd for $C_{28}H_{24}N_2O_2$ (420.49): C, 79.97; H, 5.75; N, 6.66. Found: C, 79.90; H, 5.82; N, 6.66.

3,4-Methylenedioxy-3',4'-methylenedioxybenzil Dianil (4d).—Yellow crystals, mp 127–128°, yield 95%.

Anal. Calcd for $C_{28}H_{20}N_2O_4$ (448.46): C, 74.99; H, 4.50; N, 6.25. Found: C, 74.74; H, 4.65; N, 6.21.

Benzil-4,4'-dimethyl Dianil (4e).—Yellow crystals, mp 163–164°, yield 96%.

Anal. Calcd for $C_{28}H_{24}N_2$ (388.49): C, 86.56; H, 6.23; N, 7.21. Found: C, 86.46; H, 6.15; N, 7.26.

1,3,4,5-Tetraphenylimidazolone-2 (5).—Phosgene was introduced into a solution of α,α'-dianilinostilbene (3.62 g, 10 mmol) in methylene chloride (250 ml) and pyridine (2 ml) which was agitated with a stream of nitrogen. By varying the rate of nitrogen introduction, the reaction temperature was kept between 20 and 26°. The solution first turned dark brown and then light yellow. After 1 hr the reaction mixture was diluted with 20 ml of methanol and 0.5 ml of concentrated hydrochloric acid. Vacuum evaporation of the methylene chloride and dilution of the residual methanol solution with 10 ml of water gave 3 g (77%) of colorless crystalline precipitate, mp 208–209° (lit.[10] 207°).

Anal. Calcd for $C_{27}H_{20}N_2O$ (388.45): C, 83.48; H, 5.19; N, 7.21. Found: C, 83.7; H, 5.26; N, 7.24.

Registry No.—**2e**, 24099-47-6; **3a**, 24099-48-7; **3b**, 24099-49-8; **3c**, 24099-50-1; **3d**, 24099-51-2; **3e**, 24099-52-3; **4b**, 21854-88-6; **4c**, 21854-89-7; **4d**, 24099-55-6; **4e**, 24099-56-7.

Acknowledgments.—The author is indebted to Mrs. D. V. Temple for recording ir and uv spectra, to Mr. J. D. Cargioli for recording 100-Mc nmr spectra, and to Miss W. Racela for elemental analyses.

(10) H. Biltz, *Justus Liebigs Ann. Chem.*, **368**, 156 (1909).

Reactions of *gem*-Dithio Compounds

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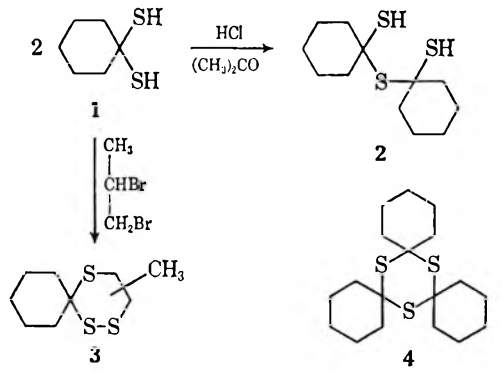
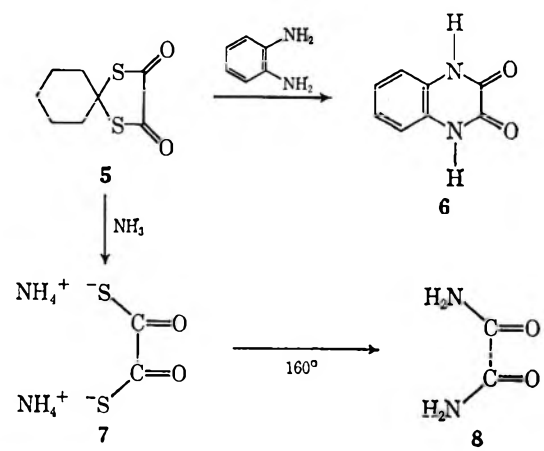
The relatively stable *gem*-dithiol function is intriguing when compared with the analogous *gem*-diols, which undergo spontaneous dehydration to yield carbonyl groups. It was our desire to further extend the interesting chemistry already reported on this system, and which often resulted from cleavage of the dithio group.[1]

Cyclohexane-1,1-dithiol (**1**) reacted in acidified acetone to yield bis(1-mercaptocyclohexyl) sulfide (**2**) in preference to a 1,3-dithietane which could arise through dithioketal formation with acetone. Compound **2** represents the dimer intermediate in the synthesis of 2,4,6-tris(pentamethylene)-1,3,5-trithiane (**4**), a known product of reaction of cyclohexane-1,1-dithiol with hydrogen chloride.[1a]

A displacement reaction between cyclohexane-1,1-dithiol and 1,2-dibromopropane in alkaline medium did not yield a dithioketal but afforded instead the trithiane **3**. This product must arise by capture of a sulfur from a second molecule of cyclohexane-1,1-dithiol.



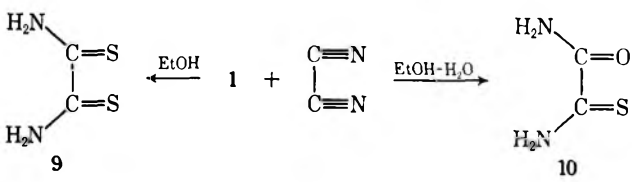
The facile cleavage of *gem*-dithio compounds was observed in the following two reactions. 2,3-Dioxyquinoxaline (**6**) formed rapidly upon admixture of equimolar amounts of 2,2-pentamethylene-1,3-dithiolane-4,5-dione (**5**) and *o*-phenylenediamine in benzene. The substitution of excess ammonia for *o*-phenylenediamine in this reaction gave as an isolable intermediate, ammonium 1,2-dithiooxalate (**7**). Ammonium 1,2-dithiooxalate gave a quantitative yield of oxamide upon being heated to 160°. Although the products isolated from the reactions of 2,2-pentamethylene-1,3-dithiolane-4,5-dione (**5**) with *o*-phenylenediamine and with ammonia suggest different reaction mechanisms, this



(1) (a) J. Jentzsch, J. Fabian and R. Mayer, *Chem. Ber.*, **95**, 1764 (1962); (b) J. Jentzsch and R. Mayer, *J. Prakt. Chem.*, **18**, 211 (1962); (c) J. Morgenstern and R. Mayer, *ibid.*, **34**, 116 (1966); (d) C. Demuynck, M. Demuynck, D. Paquer and J. Vialle, *Bull. Soc. Chim. Fr.*, 3366 (1966).

need not be the case. We assume that dithiooxalate is displaced in both instances by attack of nitrogen at the dithioketal carbon. Ammonium dithiooxalate is stable at room temperature, whereas the salt with *o*-phenylenediamine may lose hydrogen sulfide spontaneously to give 2,3-dioxyquinoxaline (**6**). When potassium dithiooxalate[2] is mixed with *o*-phenylenediamine hydrochloride in dilute hydrochloric acid, compound **6** is formed readily. Dithiooxalic acid is unstable and even its metal salts vary greatly in stability.[2]

The loss of hydrogen sulfide from cyclohexane-1,1-dithiol was observed in a capricious reaction with cyanogen. Depending on reaction conditions, rubeanic acid (dithiooxamide) (**9**) or thiooxamide (**10**) is formed.



9 **10**

Oxidation of cyclohexane-1,1-dithiol with hydrogen peroxide yielded cyclohexanone.

Experimental Section[3]

Bis(1-mercaptocyclohexyl) Sulfide (**2**).—A solution of 14.8 g of cyclohexane-1,1-dithiol[1a] in 50 ml of acetone was added to 100 ml of acetone saturated with hydrogen chloride. After 15 min. of stirring, the solvent was removed under vacuum. The residue, dissolved in ether, was washed with water until neutral. Magnesium sulfate was used to dry the solution. Evaporation of the solvent and distillation of the residue afforded 4.2 g of bis(1-mercaptocyclohexyl) sulfide (32% yield), bp 115–118° (0.9 mm). The product possessed the correct molecular weight, 262, as confirmed by mass spectroscopy. The ir spectrum was consistent with the proposed structure: ir (film) 2924, 2849, 1453, 1439, 1368, 1350, 1145, and 1120 cm^{-1}. Inspection of molecular models and comparison with the nmr data of the trithiane **4** suggested the following assignments: nmr ($CDCl_3$) δ 2.1 (m, ~4, equatorial –CHCS), 1.73 (s, ~12, 3,4,5,3′,4′,5′-CH_2) and 1.53 ppm (m, ~4, axial –CHCS). No other resonance was evident; thus the sulfhydryl protons must lie beneath the other signals and are responsible for the deviations from the calculated signal integrations.

Anal. Calcd for $C_{12}H_{22}S_3$: C, 54.90; H, 8.45; S, 36.65. Found: C, 54.76; H, 8.51; S, 36.81.

5- (or 6-) Methyl-3,3-pentamethylene-1,2,4-trithiane (**3**).—A mixture of 6.0 g of cyclohexane-1,1-dithiol,[1a] 3.4 g of sodium hydroxide and 8.5 g of 1,2-dibromopropane in 500 ml of ethanol was refluxed for 6 hr. The solvent was removed and the partially solid residue (NaBr) was extracted with ether. Evaporation of the ether yielded an oil which was distilled to give 4.0 g of product: bp 108–111° (0.4 mm) (bath temperature); ir (film) 2907, 2841, 1437, 1399, 1362, 1305, 1263, 1248, 1189, 1126, 1008, 867, and 754 cm^{-1}. The mass spectrum of this compound was consistent with the proposed structure. Peaks in evidence included the parent ion, *m/e* 220; propylcyclohexenyl sulfide carbonium ion, 155; cyclohexenethiol ion, 114; and cyclohexenyl carbonium ion, 81. The nmr spectrum of this product was too complex to allow unambiguous structural assignments. The signals occur between δ 1.1 and 3.6 ppm ($CDCl_3$). Four protons deshielded by proximity to sulfur gave a separated pattern centered at δ 3.1 ppm.

Anal. Calcd for $C_9H_{16}S_3$: C, 49.04; H, 7.32; S, 43.64. Found: C, 48.78; H, 7.57; S, 43.83.

2,3-Dioxyquinoxaline (**6**).—Admixture of two solutions of 200 mg of 2,2-pentamethylene-1,3-dithiolane-4,5-dione[1a] and of 107 mg of *o*-phenylenediamine, each in a minimum amount of benzene, yielded a precipitate immediately. The mixture was stirred for an additional 4 hr, after which 80 mg of product (50% yield) was removed by filtration, mp >300°. The ir spectrum of the product was identical with that of an authentic sample of 2,3-dioxyquinoxaline prepared by pyrolysis of a mixture of oxalic acid and *o*-phenylenediamine.[4]

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.12; H, 3.77; N, 17.12.

Ammonium Dithiooxalate (**7**) **and Oxamide** (**8**).—Gaseous ammonia was passed into a solution of 1 g of 2,2-pentamethylene-1,3-dithiolane-4,5-dione[1a] in 50 ml of benzene for 25 min. An orange precipitate developed and this was removed by filtration, 640 mg (83%) yield). An analytical sample was obtained by water–acetone recrystallization. The sample did not melt, but at 160° it was quantitatively transformed into oxamide as identified by its ir spectrum which was superimposable on that of an authentic sample.

Anal. Calcd for $C_2H_8N_2O_2S_2$: C, 15.38; H, 5.16; N, 17.93; S, 41.05. Found: C, 15.23; H, 5.22; N, 17.33; S, 41.45.

Rubeanic Acid (Dithiooxamide) (**9**).—A solution of 6.0 g of cyclohexane-1,1-dithiol in 50 ml of 95% ethanol was slowly added to a solution of 2.0 g of cyanogen in 500 ml of 95% ethanol with cooling in ice. The yellow mixture was allowed to stand at room temperature for 2 days. The solvent was removed and the residue was triturated first with cyclohexane and then with methanol. An orange powder weighing 900 mg was obtained (40% yield).[5] The material darkened from orange to black between 180 and 210° (reported decomposition at about 200°[6]). The ir spectrum of the product was identical with that of an authentic sample of rubeanic acid. The mass spectrum showed the correct molecular ion at *m/e* 120.

Anal. Calcd for $C_2H_4N_2S$: C, 19.98; H, 3.35. Found: C, 20.26; H, 3.54.

Thiooxamide (**10**).—A solution of 8.0 of cyclohexane-1,1-dithiol dissolved in alcohol–water (3:1) was slowly added to a solution of 3.0 g of cyanogen in 400 ml of 95% ethanol cooled in ice. The mixture was allowed to stand at room temperature overnight. The solvent was removed and the residue was recrystallized from acetone–chloroform. This material (3.2 g) was approximately 95% pure by tlc [silica gel G, ethyl acetate–benzene (3:2)]. The ir spectrum of this sample was satisfactory but several more recrystallizations were necessary to produce an analytically pure sample, mp 180° dec (reported[7] 179–181°). The molecular weight of the product, 104, was confirmed by mass spectrometry.

Anal. Calcd for $C_2H_4N_2OS$: C, 23.07; H, 3.87; N, 26.90. Found: C, 22.98; H, 4.05; N, 26.97.

Cyclohexanone.—A solution of 14.8 g of cyclohexane-1,1-dithiol in 160 ml of 5% aqueous sodium hydroxide was cooled in ice while 200 ml of 6% aqueous hydrogen peroxide was slowly added. The excess hydrogen peroxide was decomposed with sodium thiosulfate. The solution was extracted with chloroform and the extract was dried over magnesium sulfate. Evaporation of the solvent left 4.3 g of cyclohexanone (44% yield) as confirmed by its ir absorption spectrum and its retention time on glc (5 ft × 10% Carbowax column) on comparison with authentic samples.

Registry No.—**2**, 24265-66-5; **6**, 15804-19-0; **7**, 24265-68-7; **8**, 471-46-5; **9**, 79-40-3.

(2) H. O. Jones and H. S. Tasker, *J. Chem. Soc.*, **95**, 1904 (1909).

(3) All melting points were determined with a Mettler FPI melting point apparatus equipped with a Bausch and Lomb VOM 5 recorder. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. A Varian A-60 spectrometer was used to obtain the nmr spectra with tetramethylsilane as the internal standard. The mass spectra were determined on a Consolidated Electrodynamics Corp. Model 21-103C spectrometer at 70 eV.

(4) O. Hinsberg, *Chem. Ber.*, **41**, 2031 (1908).

(5) The theoretical yield of this reaction is calculated on the assumption that only 1 mol of hydrogen sulfide is lost from cyclohexane-1,1-dithiol. The reaction might be better performed by changing the reactant ratio so that the reaction would occur between 2 mol of cyclohexane-1,1-dithiol and 1 mol of cyanogen. The ratio used was chosen in an attempt to produce a 1:1 adduct between the reactants.

(6) P. G. Stecher, Ed., "The Merck Index," 8th ed, Merck and Co., Inc., Rahway, N. J., 1968, p 924.

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Aluminum Chloride Catalyzed Formation of Arylamides. A Novel Synthesis[1]

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Several general methods for the aluminum chloride catalyzed synthesis of aromatic amides have been reported.[2] Gattermann allowed carbamyl chloride to react with aromatic compounds to give the corresponding amides. The major disadvantage of the Gattermann synthesis was the instability of carbamyl chloride. Hopff overcame this difficulty by using stable addition compounds of carbamyl chloride with aluminum chloride. Leuckart was also able to synthesize a variety of aromatic amides by the reaction of aryl isocyanates with hydrogen chloride followed by reaction of the resulting arylcarbamyl chloride with the appropriate aromatic compound. Carboxyamidation with cyanic acid or potassium cyanate and hydrogen chloride, in which unstable carbaminic chloride is formed *in situ*, has also been used for arylamide synthesis.

A plausible reaction course (Scheme I), which is an extension of the Hopff mechanism,[2] is proposed for the carboxyamidation of benzene. Urea reacts with aluminum chloride to produce a urea–aluminum chloride adduct (1). This intermediate is decomposed on heating to give carbaminic chloride (2) and an aluminum chloride salt (3). Carbaminic chloride then reacts with aluminum chloride to provide the reactive carbonium ion (4), which attacks the aromatic nucleus in the conventional manner to give benzamide (5). Several investigators have reported the presence of cyanuric acid in the thermal-decomposition products of urea.[5,6] It is therefore not surprising that a carbaminic carbonium ion would be generated during the exothermic reaction of urea with anhydrous aluminum chloride.

The postulated intermediate (1) has not been reported in the literature and we have not attempted to characterize it. There was evidence of existence of ammono aluminum chloride (3) because ammonia was evolved when the aqueous solutions of these salts were neutralized.

The arylamides (Table I) contained *ortho*- and *para*-orientating groups on the aromatic nucleus, but owing to the stronger *para*-orientating groups and to the low yields, only the *para*-substituted amides were isolated.

TABLE I
ARYLAMIDES

Amide	Mp, °C			%	Calcd, %				Found, %			
	Literature	Reference[a]	Found	yield	C	H	N	X	C	H	N	X
Benzamide	130	IX, 195	128–129	6	69.40	5.83	11.56		69.62	6.06	11.26	
4-Chlorobenzamide	179	IX, 341	179–180	2	54.02	3.89	8.99	22.81	54.06	4.11	9.15	22.93
4-Fluorobenzamide	154.5	IX–I, 137	156–157	6	60.43	4.35	10.06	13.30	60.67	4.34	9.93	13.42
4-Hydroxybenzamide	162	X, 164	151–152	13	61.31	5.15	10.21		61.54	4.99	10.38	
4-Phenylbenzamide	222–223	IX, 672	229–230	27	79.16	5.62	7.10		79.00	5.53	7.19	
4-Methylbenzamide	159–160	IX, 486	157–158	4	71.09	6.71	10.36		71.10	6.62	10.08	
3-Chloro-4-methylbenzamide		*b*	162–163	14	56.63	4.75	8.26	20.93	56.58	4.64	8.07	20.64
3,4-Dimethylbenzamide	130–131	IX, 536	105–106	9	72.46	7.43	9.38		72.45	7.47	9.50	
2,4,6-Trimethylbenzamide	187–188	IX, 553	190–191	25	73.59	8.03	8.58		73.64	8.00	8.40	
4-Methoxybenzamide	166.5–167.5	X, 164	167–168	22	63.56	6.00	9.27		63.47	5.98	9.24	

[a] "Beilstein's Handbuch," 4th ed, Julius Springer Verlag, Berlin 1926–1927. [b] Not found in the literature.

While a urea–aluminum chloride solvent system for the reaction of carbohydrates with aromatic compounds was being investigated, unexpected crystalline by-products were isolated. Purification and characterization of these compounds revealed that arylamides had been formed by a novel route that utilized urea as the carboxyamidating agent.

Addition of urea to anhydrous aluminum chloride results in an exothermic reaction, and in formation of a fluid system which has been used as a solvent-catalyst for various chemical reactions.[3,4] We have synthesized 10 arylamides (Table I) by reaction between the appropriate aromatic compounds and this urea–aluminum chloride solution.

The melting point of 3,4-dimethylbenzamide (105–106°) differs significantly from the literature value (130–131°); however the elemental analysis of the amide (Table I) is in agreement with the empirical formula. The only other structural alternative would be 2,3-dimethylbenzamide,[7] which has an even higher melting point (155–156°). In view of these data we hydrolyzed the low melting 3,4-dimethylbenzamide and identified the product as 3,4-dimethylbenzoic acid. Isolation of this acid verified that the assigned structure of 3,4-dimethylbenzamide was correct.

In the present investigation no attempts were made to maximize the yields of aromatic amides.

(1) Sponsored by the Nebraska Department of Agriculture and Economic Development.

(2) G. A. Olah, "Friedel–Crafts and Related Reactions," Vol. 3, Part 2, Wiley-Interscience, New York, N. Y., 1964, p 1262.

(3) W. Braun, German Patent 878,647 (June 5, 1953); *Chem. Abstr.*, **50**, 4203*a* (1956).

(4) W. Braun, German Patent 1,085,514 (July 21, 1960); *Chem. Abstr.*, **55**, 16490*i* (1961).

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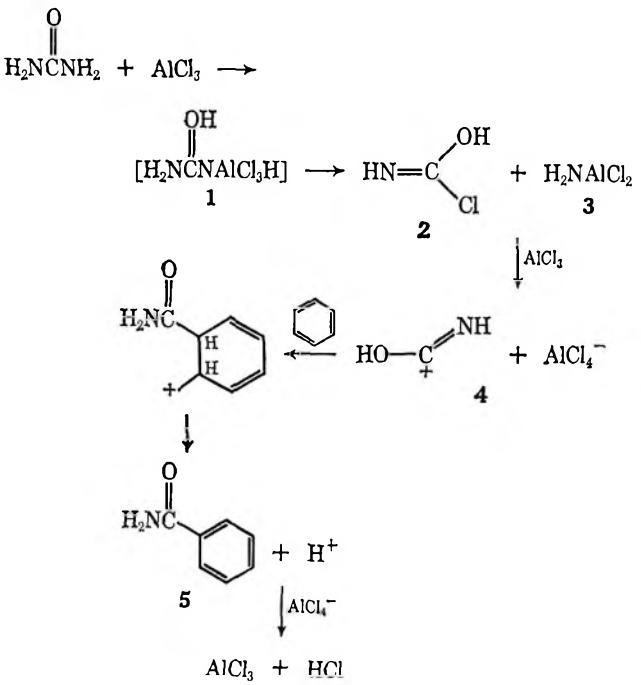
(7) T. Terakawa, H. Ouchi, H. Zenno, K. Nakanishi, and S. Umio, *J. Pharm. Soc. Jap.*, **74**, 312 (1954); *Chem. Abstr.*, **49**, 3078*h* (1955).

SCHEME I



Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. Melting points were uncorrected and obtained by using a Hoover capillary melting point apparatus.

Synthesis of Arylamides.—The general method for the preparation of these compounds was as follows. Urea, 24 g (0.40 mol), was carefully added to 113 g (0.85 mol) of anhydrous aluminum chloride. Care must be exercised during this addition because an exothermic reaction results. The temperature of the reaction was controlled by the rate of urea addition. However, the reaction temperature was usually kept in the range of 90–100°. After the addition of the urea was complete, the resulting mixture was cooled to 25° and 0.35 mol of the appropriate aromatic compound was added. The reactants were stirred for 2–18 hr at 50–70°, cooled, and slowly poured into 500 ml of ice water. Because substantial amounts of unchanged aluminum chloride are present in the reaction mixture, extreme care must be exercised while decomposing it in the ice water. Pentane (500 ml) was added, and the two phases filtered. Arylamides which are water- and pentane-insoluble remain as a solid on the filter paper. Water-soluble arylamides (*e.g.*, 4-methylbenzamide) were ether extracted from the water phase. The ether extracts were dried over anhydrous calcium sulfate, the ether was evaporated, and the residues were recrystallized from benzene or water to give pure arylamides.

Properties of Arylamides.—The arylamides were characterized by their elemental analyses, infrared spectra, and comparisons of their respective melting points with literature values.

Table I summarizes the results of the elemental analyses and the comparative melting point data. The infrared spectra of the arylamides exhibited the following characteristic absorption bands: ir (Nujol) 3450–3320 cm^{-1} (free NH), 3210–3160 cm^{-1} (associated NH), 1660–1640 cm^{-1} (amide I band), 1620–1610 cm^{-1} (amide II band), and 1560 cm^{-1} (phenyl nucleus).

Hydrolysis of 3,4-Dimethylbenzamide.—A mixture of 200 mg (1.30 mmol) of 3,4-dimethylbenzamide, mp 105–106° (Table I), and 10 ml of 3 *N* NaOH was heated at reflux for 6 hr, cooled, and acidified with 4 ml of concentrated HCl to give 192 mg of crude acid, mp 152–156°. Sublimation of this material at 60° *in vacuo* afforded 163 mg (82%) of 3,4-dimethylbenzoic acid, mp 162–163°; ir spectrum was identical with that of 3,4-dimethylbenzoic acid.[8]

(8) "Sadtler Standard Spectra," No. 24490, Microfilm Edition, Sadtler Research Laboratories, Inc., 1969.

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.48; H, 6.67.

Registry No.—Aluminum chloride, 7446-70-0; 3-chloro-4-methylbenzamide, 24377-95-5.

The Oxidation of 2,6-Disubstituted Phenols with Isoamyl Nitrite. A Simple Preparation of Diphenoquinones

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Phenol oxidation by alkyl nitrites has not been extensively studied. The reported oxidations have been concerned chiefly with 2,4,6-trisubstituted compounds.[2] In Bacon's survey of oxidants for 2,6-dimethylphenol, the reaction of isoamyl nitrite (60 mol) with phenol (1 mol) in water gave 2,2′,6,6′-tetramethyl-4,4′-biphenol (20%) and 3,3′,5,5′-tetramethyldiphenoquinone (37%).[3] When the mole ratio was reduced to 7.5:1 in ethyl alcohol, the diphenoquinone (6%) was obtained along with the major product, *p*-nitroso-2,6-dimethylphenol (75%).

We have extended this oxidation to a convenient synthesis of certain diphenoquinones by oxidation of 2,6-disubstituted phenols with isoamyl nitrite in methylene chloride. The reaction is run for 18–24 hr at ambient temperature and the insoluble product is isolated by filtration. Table I gives the results for a number of phenols; yields are in the 50–65% range. When sterically hindering groups such as *t*-butyl or deactivating groups such as chlorine occupy the *ortho* positions, the yields are lower. The higher oxidation potential of 2,6-dichlorophenol completely inhibited its oxidation to the diphenoquinone whereas 2-chloro-6-phenylphenol gave a small yield of quinone. The yields were improved by using chloroform at reflux for 2.5 hr.

TABLE I

2,6-Disubstituted phenol	Diphenoquinone: % yield of CH_2Cl_2	Diphenoquinone: Mp, °C	Mol of oxidant/mol of phenol
Dimethyl-	53[a]	205.5–208[b]	2.1
Diphenyl-	58	283–285[b]	3.0
Methyl phenyl-	51	202–204[b]	2.5
Dimethoxy-	65	288–290[b]	2.5
Di-*t*-butyl-	16	242.5–244[b]	3.3
Chloro phenyl-	10[c]	287.5–288.5	3.0
Dichloro-			

[a] 64% yield obtained in $CHCl_3$. [b] The infrared spectrum was identical with that of the authentic material. [c] 21% yield obtained in $CHCl_3$.

(1) Food and Drug Administration, Bureau of Drugs, Washington, D. C. 20204.

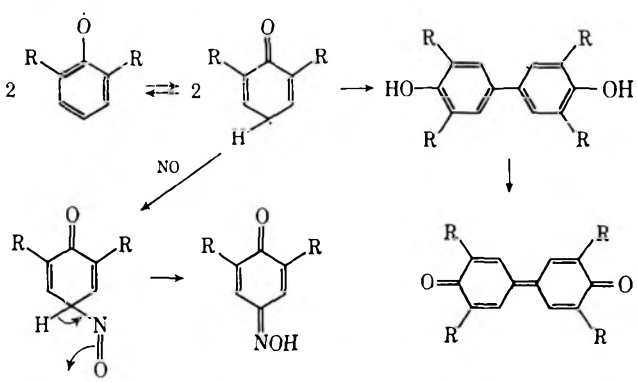
(2) (a) J. Thiele and H. Sichwerde, *Ann.*, **311**, 363 (1900). (b) V. V. Ershov and G. A. Zlobina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2138 (1964).

(3) R. G. R. Bacon and A. R. Izzat, *J. Chem. Soc.*, 791 (1966).

The reduction in yield when a *t*-butyl group is present is probably due to two factors: the increased solubility of diphenoquinones containing such groups and competing oximination. The isolation of 2,6-di-*t*-butyl-4-oximinobenzoquinone, which has been reported both as *p*-nitroso-2,6-di-*t*-butylphenol[4] or as the oxime,[5] and recently has been shown to exist as the oxime,[6] from the oxidation of 2,6-di-*t*-butyl phenol supports the second factor.

The reaction path very likely involves the production of phenoxy radicals. Ershov and Zlobina were able to record the esr signal for 2,4,6-trisubstituted phenoxy radicals when the corresponding phenols were oxidized with alkyl nitrites.[2b] They proposed that an alkoxy radical, produced by scission of the alkyl nitrite, abstracted hydrogen from the phenol to give the phenoxy radical. Some support for the intermediacy of an alkoxy radical is contained in the thermal decomposition of 2-octyl nitrite at 100°.[7] The products are the 2-octyloxy and the nitric oxide radicals. In the case of the 2,6-disubstituted phenols in Table I, the free *para* positions would allow dimerization to the biphenol.[8] Subsequent oxidation of the biphenol would give the diphenoquinone, Scheme I. The total process involves the removal of two hydrogen atoms from each mole of phenol to give the diphenoquinone, necessitating at least 2 mol of oxidant/mol of phenol. The formation of oxime in the case of 2,6-di-*t*-butylphenol can be explained by the combination of nitric oxide and phenoxy radicals (Scheme I).

SCHEME I



Experimental Section[9]

3,3′,5,5′-Tetramethyl-4,4′-diphenoquinone.—An example of the general method is given for 2,6-dimethylphenol. 2,6-Dimethylphenol (1.83 g, 0.015 mol) was dissolved in 50 ml of methylene chloride and isoamyl nitrite added (4.3 ml, 0.032 mol). After stirring at ambient temperature for 24 hr, the reaction was worked up by cooling and filtering. The red crystals obtained were washed with several portions of cold methylene chloride and dried to give 0.976 g of product (53%), mp 205.5–208° (lit.[10] mp 207–210°). The ir spectrum was essentially identical with that of the authentic material.

3,3′,5,5′-Tetra-*t*-butyl-4,4′-diphenoquinone.—2,6-Di-*t*-butylphenol (3.09 g, 0.015 mol) and isoamyl nitrite (6.72 ml, 0.050 mol) were dissolved in 20 ml of methylene chloride. The solution was stirred at ambient temperature for 28 hr and then heated at reflux for 15 hr. The solvent was distilled to leave a semisolid mass. This was treated with acetic acid and filtered. The filter cake was washed with acetic acid and dried to give 0.503 g of title compound (16.3%), mp 242.5–244° (lit.[11] mp 245–247°). The ir spectrum was essentially identical with that of the authentic material.

2,6-Di-*t*-butyl-4-oximino-*p*-benzoquinone.—2,6-Di-*t*-butylphenol (3.09 g, 0.015 mol) was dissolved in 25 ml of methylene chloride and isoamyl nitrite (5.10 ml, 0.0375 mol) was added. The reaction solution was stirred at ambient temperature for 27 hr and then the solvent was removed under vacuum (20 mm). The gummy dark residue was treated with 20 ml of methyl alcohol and filtered to remove some brown solid. The filtrate was warmed under vacuum to remove the solvent and the dark oil which remained was extracted with hot hexane. The hexane was concentrated and cooled to give 0.273 g of yellow crystals, mp 205–207°. Further hexane extraction of the dark gum gave an additional 0.370 g of yellow crystals, mp 199–205°. The two batches were combined and recrystallized from hexane to give 0.630 g (18%) of title compound, mp 213–214° (lit.[5] mp 219–220°). The ir spectrum contained a broad band at 3320 cm^{-1} (–OH) and a sharp band at 1600 cm^{-1} (C=N).

3,3′-Dichloro-5,5′-diphenyl-4,4′-diphenoquinone.—2-Chloro-6-phenylphenol (2.04 g, 0.01 mol) was dissolved in 22 ml of methylene chloride and isoamyl nitrite was added (4.0 ml, 0.03 mol). The solution was stirred at ambient temperature for 24 hr at which time some red solid was present. The mixture was heated at reflux for 2 hr, cooled, and filtered. The filter cake was washed with cold methylene chloride and dried under vacuum to give purple-red crystals, 0.21 g (10%), mp 282–283°. This was recrystallized from chloroform to give mp 287.5–288.5°; ir (KBr) 1610 cm^{-1} (C=O). *Anal.* Calcd for $C_{24}H_{14}Cl_2O_2$: C, 71.13; H, 3.48; Cl, 17.50. Found: C, 70.5; H, 3.77; Cl, 17.7.

Registry No.—Isoamyl nitrite, 110-46-3; 2,6-dimethylphenol, 576-26-1; 2,6-diphenylphenol, 2432-11-3; 2-methyl-6-phenylphenol, 17755-10-1; 2,6-dimethoxyphenol, 91-10-1; 2,6-di-*t*-butylphenol, 128-39-2; 2-chloro-6-phenylphenol, 85-97-2; 2,6-dichlorophenol, 87-65-0; 3,3′-dichloro-5,5′-diphenyl-4,4′-diphenoquinone, 24378-09-4.

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β-Keto Sulfoxides. IX. Conversion into Acetylenic Sulfoxides and Sulfones[1]

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We have previously described the conversion of esters to β-keto sulfoxides (reaction 1)[2] and the reduction of the β-keto sulfoxide to the hydroxy sulfide (reaction 2),[3] which may be dehydrated to give the vinyl sulfide (reaction 3).[3] Attempts to convert β-(methylmercapto)styrene to the acetylenic sulfide by the standard bromination–dehydrobromination technique[4]

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(3) G. A. Russell, E. Sabourin, and J. Mikol, *J. Org. Chem.*, **31**, 2854 (1966).
(4) W. E. Truce, H. E. Hill, and M. M. Boudakian, *J. Amer. Chem. Soc.*, **78**, 2760 (1956).

gave in our hands only a 13% yield of methyl phenethynyl sulfide. We have therefore developed an alternate method (reactions 4–6) for converting a vinyl sulfide into an acetylenic sulfide using the previously described reactions 5 and 6.[3]

$$RCO_2Et + CH_3SOCH_2^- \longrightarrow RCOCH_2SOCH_3 + EtO^- \quad (1)$$

$$RCOCH_2SOCH_3 \xrightarrow{LiAlH_4} RCH(OH)CH_2SCH_3 \quad (2)$$

$$RCH(OH)CH_2SCH_3 \xrightarrow{H^+,\ \Delta} RCH{=}CHSCH_3 \quad (3)$$

$$RCH{=}CHSCH_3 \xrightarrow{NaIO_4} RCH{=}CHSOCH_3 \quad (4)$$

$$RCH{=}CHSOCH_3 \xrightarrow{SOCl_2} RC(Cl){=}CHSCH_3 \quad (5)$$

$$RC(Cl){=}CHSCH_3 \xrightarrow[EtOH]{KOH} RC{\equiv}CSCH_3 \quad (6)$$

$$RC{\equiv}CSCH_3 \xrightarrow{m\text{-}ClC_6H_4CO_3H} RC{\equiv}CSOCH_3 \xrightarrow{[O]} RC{\equiv}CSO_2CH_3 \quad (7)$$

The oxidation of vinyl sulfides to vinyl sulfoxides is complicated by epoxidation of the double bond and the possibility of overoxidation to yield the sulfone. We have found that a selective oxidation of a vinyl sulfide to a vinyl sulfoxide can be achieved using sodium metaperiodate in a modification of the procedure of Leonard and Johnson.[5] Nearly quantitative yields of vinyl sulfoxides can be obtained by the use of 0.5 *M* sodium metaperiodate in 50% aqueous acetonitrile solution at −10°. An alternate procedure, which is greatly preferred for the conversion of acetylenic sulfides to acetylenic sulfoxides, is to use 1 equiv of *m*-chloroperbenzoic acid at −20° in chloroform solution.[6] Table I summarizes some pertinent results.

TABLE I

CONVERSION OF SULFIDES TO SULFOXIDES

	Yield (%) of sulfoxide	
Sulfide	$NaIO_4$	*m*-$ClC_6H_4CO_3H$
$C_6H_5CH{=}CHSCH_3$	77[a]	
$C_6H_5C{\equiv}CSCH_3$	46	92
$C_6H_5CH{=}C(CH_3)SCH_3$	74	
$C_6H_5C(Cl){=}CHSCH_3$	73	
$(C_6H_5)_2C{=}CHSCH_3$	96	79
$(C_6H_5)_2C{=}C(SCH_3)_2$	96	97
$C_6H_5C(CH_3){=}C(SCH_3)_2$	90	90
$C_6H_5C(C_2H_5){=}C(SCH_3)_2$	68	86

[a] See ref 3.

m-Chloroperbenzoic acid (2 equiv) is the preferred reagent to convert methyl phenethynyl sulfide to the sulfone (81% yield). Use of hydrogen peroxide in acetic acid[4,7] led only to a polymer under the conditions reported to be satisfactory for the oxidation of phenyl phenethynyl sulfide.

β,β-Di(methylmercapto)styrene reacted with either sodium metaperiodate or *m*-chloroperbenzoic acid to yield a rearrangement product [S-methyl α-(methylmercapto)phenylthioacetic acid] probably the result of epoxidation of the double bond.[1]

$$C_6H_5CH{=}C(SCH_3)_2 \xrightarrow{[O]} [C_6H_5CH(O)C(SCH_3)_2] \longrightarrow C_6H_5\overset{+}{C}H{-}C(SCH_3)_2(O^-) \longrightarrow C_6H_5CH(SCH_3)COSCH_3$$

An alternate reaction sequence to reactions 6 and 7 is to first oxidize the chloro vinyl sulfide to the sulfoxide and then dehydrohalogenate (reactions 8 and 9).

$$C_6H_5C(Cl){=}CHSCH_3 \xrightarrow{[O]} C_6H_5C(Cl){=}CHSOCH_3 \quad (8)$$

$$C_6H_5C(Cl){=}CHSOCH_3 \xrightarrow[THF]{KOC(CH_3)_3} C_6H_5C{\equiv}CSOCH_3\ (89\%) \quad (9)$$

$$C_6H_5C(Cl){=}CHSOCH_3 \xrightarrow[THF]{NaOC_2H_5} C_6H_5C(OC_2H_5){=}CHSOCH_3\ (86\%) \quad (10)$$

Use of potassium *t*-butoxide in THF, a base with low nucleophilicity, led to methyl phenethynyl sulfoxide in high yield, whereas a nucleophilic base, such as sodium ethoxide, led to the α-ethoxy-β-(methylsulfinyl)styrene. Ethoxide ion is known to add readily to acetylenic sulfides[8] and will presumably add even more readily to acetylenic sulfoxides.

Experimental Section[9]

Oxidation Techniques.—The sodium metaperiodate oxidations were performed by mixing at −10° 60 ml of a acetonitrile solution containing 25 mmol of the sulfide with 60 ml of a 0.5 *M* aqueous solution of sodium metaperiodate. The solution was stirred in a refrigerator at −5 to −10° for 12 hr, whence the cold solution was filtered and extracted three times with 50-ml portions of chloroform. The dry chloroform extracts ($MgSO_4$) were concentrated under vacuum to yield the crude sulfoxides that were purified by column chromatography or crystallization.

For the *m*-chloroperbenzoic acid oxidations, the vinyl sulfide (25 mmol) in 100 ml of chloroform was cooled to −10° and 1 equiv of analyzed *m*-chloroperbenzoic acid[10] in 50 ml of chloroform at −10° was added slowly. The reaction flask was stoppered and allowed to stand at −23° in a refrigerator for 12 hr. The cool solution was filtered to remove *m*-chlorobenzoic acid, washed twice with 100 ml of saturated aqueous sodium bicarbonate, and dried ($MgSO_4$); the solvent was removed under vacuum to yield the crude sulfoxide.

Sulfoxides.—The vinyl sulfides listed in Table I have been previously described,[1,3] as has **β-(methylsulfinyl)styrene.**[3] **1-(Methylsulfinyl)-2,2-diphenylethylene** was crystallized from 1:1 hexane–ether to yield material: mp 106°; pmr δ 2.72 (s, 3, $SOCH_3$), 6.81 (s, 1, =CH–), δ 7.15–7.55 (m, 10, C_6H_5).

Anal. Calcd for $C_{15}H_{14}OS$: C, 74.36; H, 5.83; S, 13.21. Found: C, 74.10; H, 5.92; S, 13.21.

β-Methyl-β-(methylsulfinyl)styrene was crystallized from 1:4 ethyl acetate–hexane to give mp 103–104°; pmr δ 2.63 (s, 3, $SOCH_3$), 2.21 (d, 3, CH_3, J = 2 Hz), 7.10 (q, 1, =CH–, J = 2 Hz), 7.32 (s, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{12}OS$: C, 66.65; H, 6.71; S, 17.76. Found: C, 66.75; H, 6.60; S, 17.93.

α-Chloro-β-(methylsulfinyl)styrene was purified by column chromatography on silica gel. Impurities were eluted by ethyl acetate and the sulfoxide was recovered by elution with methanol. Evaporation of the methanol gave a product that was recrystallized from 1:1 ethyl acetate–hexane to give the sulfoxide: mp 85–86°; pmr δ 2.80 (s, 3, $SOCH_3$), 6.98 (s, 1, =CH–), 7.30–7.80 (m, 5, C_6H_5).

Anal. Calcd for C_9H_9ClOS: C, 53.86; H, 4.52; S, 15.97; Cl, 17.66. Found: C, 54.01; H, 4.50; S, 16.02; Cl, 17.74.

α-Methyl-β-(methylsulfinyl)styrene was prepared from a mixture of 9 parts of *cis*- to 1 part of *trans*-α-methyl-β-(methylmercapto)styrene[3] (*cis* and *trans* refer to the relationship of the phenyl and thiomethyl groups). The crude product appeared

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(9) Pmr spectra were obtained in $CDCl_3$ at 60 MHz. Mass spectra were obtained by direct inlet into an Atlas Werke CH-4 spectrometer.

(10) Material from the Research Organic/Inorganic Chemical Co., Sun Valley, Calif., was used in this work; assay, 83% peracid.

to be a mixture of the *cis* and *trans* sulfoxides in ~9:1 ratio. Column chromatography on silica gel with ethyl acetate eluent gave material that could be crystallized from 4:1 hexane–ethyl acetate to yield material with mp 28–34°. Pmr: predominant isomer (90%), δ 2.68 (s, 3, $SOCH_3$), 2.39 (d, 3, CH_3, J = 1.5 Hz), 6.67 (q, 1, =CH–, J = 1.5 Hz); minor isomer (10%), δ 2.61 (s, 3, $SOCH_3$), 2.28 (d, 3, CH_3, J = 2.5 Hz), 6.40 (q, 1, =CH–, J = 2.5 Hz).

Anal. Calcd for $C_{10}H_{12}OS$: C, 66.65; H, 6.71; S, 17.76. Found: C, 66.83; H, 6.76; S, 17.88.

α-Ethyl-β-(methylsulfinyl)styrene was prepared from a mixture of 8 parts of *cis*- and 2 parts of *trans*-α-ethyl-β-(methylmercapto)-styrene[3] (*cis* and *trans* refer to the relationship of the phenyl and thiomethyl groups). The nearly pure crude product was chromatographed from silica gel by ethyl acetate to remove traces of more and less mobile impurities to give an oil which contained approximately 80% *cis* sulfoxide and 20% *trans* sulfoxide. Pmr: predominant isomer (80%), δ 2.67 (s, 3, $SOCH_3$), 6.46 (s, 1, =CH–); minor isomer (20%), δ 2.58 (s, 3, $SOCH_3$); 6.32 (t, 1, =CH–, J = 2 Hz). The ethyl groups and aryl groups gave pmr multiplets centered at δ 1.07, 2.85, and 7.3.

Anal. Calcd for $C_{11}H_{14}OS$: C, 68.02; H, 7.27; S, 16.47. Found: C, 67.99; H, 7.43; S, 16.32.

1-(Methylsulfinyl)-1-(methylmercapto)-2,2-diphenylethylene was recrystallized from 1:1 ethyl acetate–hexane to give material: mp 108–110°; pmr δ 2.24 (s, 3, SCH_3), 2.73 (s, 3, $COCH_3$), 7.10–7.45 (broad s, 10, C_6H_5).

Anal. Calcd for $C_{16}H_{16}OS_2$: C, 66.66; H, 5.59; S, 22.20. Found: C, 66.39; H, 5.41; S, 22.49.

β-(Methylsulfinyl)-β-(methylmercapto)-α-methylstyrene was recrystallized from 4:1 hexane–ether to give material, mp 101–102°, apparently a single stereoisomer: pmr δ 2.15 (s, 3, CH_3), 2.40 (s, 3, SCH_3), 2.62 (s, 3, $SOCH_3$), 7.00–7.45 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.40; H, 6.24; S, 28.29. Found: C, 58.56; H, 6.02; S, 28.30.

β-(Methylsulfinyl)-β-(methylmercapto)-α-ethylstyrene was crystallized from 4:1 hexane–ether to give crystals, mp 82–84°, apparently a single stereoisomer: pmr δ 0.99 (t, 3, CH_2CH_3, J = 7.5 Hz), 2.58 (broad s, 6, SCH_3, $SOCH_3$, Δδ = 0.8 Hz), 2.94 (q, 2, CH_2CH_3, J = 7.5 Hz), 6.95–7.45 (m, 5, C_6H_5).

Anal. Calcd for $C_{12}H_{16}OS_2$: C, 59.99; H, 6.71; S, 26.64. Found: C, 60.00; H, 6.62; S, 26.62.

α-Chloro-β-(methylsulfinyl)styrene[3] (Reaction 5).—α-(Methylmercapto)styrene (20 g, 120 mmol) in 100 ml of methylene chloride was treated with 18 ml (250 mmol) of thionyl chloride dissolved in 20 ml of methylene chloride. The thionyl chloride solution was added dropwise at a rate sufficient to maintain reflex. After addition of the thionyl chloride the mixture was stirred for 4 hr at 25°. Removal of the solvent under vacuum left a brown oil which was dissolved in 300 ml of hexane and washed twice with 100 ml of 10% $NaHCO_3$ and dried over $MgSO_4$. Distillation yielded 17.5 g (79%) of the chloro sulfide: bp 76–82° (0.2 Torr); pmr ($CDCl_3$) δ 2.45 (s, 3, SCH_3); 6.60 (s, 1, –CH=), 7.18–7.55 (m, 5, C_6H_5); ir (neat) 1670 cm^{-1} (C=C).

Methyl Phenethynyl Sulfide (Reaction 6).—α-Chloro-β-(methylsulfinyl)styrene (39 g, 0.21 mol) in 150 ml of ethanol was added dropwise to a mixture of 29 g of KOH (0.5 mol) in 100 ml of ethanol. The mixture was refluxed overnight and filtered, and the solvent was evaporated by use of a water aspirator. The residue was distilled to give 23 g (63%) of material boiling at 85–87° (2 Torr), lit.[11] bp 74° (2 Torr).

Reactions 5 and 6 can be combined into a single operation. Thus, the crude chloro sulfide obtained from 175 mmol of ω-(methylmerapto)styrene upon removal of the methylene chloride was dissolved in 50 ml of ethanol and added to a mixture of 25 g of KOH in 200 ml of ethanol. After stirring for 12 hr at 60° the reaction was filtered and concentrated under vacuum. Dilution with 100 ml of H_2O was followed by extraction twice with 200-ml portions of *n*-hexane and drying over $MgSO_4$; distillation yielded 17 g (67%) of methyl phenethynyl sulfide.

Methyl Phenethynyl Sulfoxide (Reaction 7).—The sulfoxide was best prepared by oxidation of the sulfide with *m*-chloroperbenzoic acid as described earlier. The sulfoxide was isolated by removal of the chloroform solvent at room temperature under vacuum. The product was eluted from a 2.5 × 50 cm silica gel column by 1.5:1 ethyl acetate–hexane as a colorless oil which polymerized upon standing: ir (CCl_4) 1060 (S=O), 2210 (C≡C) cm^{-1}; pmr (60 MHz, $CDCl_3$) δ 2.98 (s, 3, $SOCH_3$), 7.2–7.6 (m, 5, C_6H_5).

Anal. Calcd for C_9H_8OS: C, 65.58; H, 4.91; S, 19.49. Found: C, 65.70; H, 5.03; S, 19.54.

Methyl Phenethynyl Sulfone.—Methyl phenethynyl sulfide (2.96 g, 20 mmol) was dissolved in 100 ml of chloroform and cooled to −10°. A solution of 7.9 g of 83% *m*-chloroperbenzoic acid in 100 ml of chloroform at −10° was added slowly to the sulfide, and the mixture was allowed to stand for 4 days at −20°. The *m*-chlorobenzoic acid was filtered from the cool solution, and the chloroform solutions were washed twice with 100 ml of saturated sodium bicarbonate and dried ($MgSO_4$); the solvent was removed under vacuum. The residue was crystallized from 2:1:7 ethyl acetate–ether–hexane to yield 2.88 g (81%) of crystals: mp 59–60° (recrystallization from 1:1 ether–hexane raised this to 61–62°); ir (KBr) 1308 (SO_2), 1145 (SO_2), 1125 (SO_2), 2180 (C≡C) cm^{-1}; pmr δ 3.30 (s, 3, SO_2CH_3); 7.25–7.75 (m, 5, C_6H_5).

Anal. Calcd for $C_9H_8O_2S$: C, 60.00; H, 4.48; S, 17.77. Found: C, 60.11; H, 4.48; S, 17.58.

Dehydrochlorination of α-Chloro-β-(methylsulfinyl)styrene (Reaction 9).—Reaction of 2.0 g (10 mmol) of the chloro sulfoxide with 2.3 g (200 mmol) of potassium *t*-butoxide in 100 ml of THF for 15 hr at 25° led to 1.31 g (89.3%) of methyl phenethynyl sulfoxide. The acetylenic sulfoxide was isolated by pouring the reaction mixture into 200 ml of ice–water followed by extraction with three 75-ml portions of chloroform. The chloroform extracts were washed with water and dried ($MgSO_4$) and the solvent was removed under vacuum.

α-Ethoxy-β-(methylsulfinyl)styrene (Reaction 10).—Treatment of 2.00 g (10 mmol) of α-chloro-β-(methylsulfinyl)styrene in 100 ml of THF with 200 mmol of sodium ethoxide yielded a crude oil that was chromatographed to yield 1.80 g (86%) of α-ethoxy-β-(methylsulfinyl)styrene: pmr δ 2.70 (s, 3, $SOCH_3$), 1.30 (t, 3, CH_2CH_3, J = 8 Hz), 3.97 (q, 2, CH_2CH_3, J = 8 Hz), 6.02 (s, 1, =CH–), 7.30–7.65 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71; S, 15.22. Found: C, 62.62; H, 6.86; S, 15.13.

Registry No.—1-(Methylsulfinyl)-2,2-diphenylethylene, 21147-11-5; β-methyl-β-(methylsulfinyl)styrene, 24378-01-6; α-chloro-β-(methylsulfinyl)styrene, 24377-96-6; α-methyl-β-(methyl-sulfinyl)styrene (*cis*), 24377-97-7; α-methyl-β-(methylsulfinyl)styrene (*trans*), 24377-98-8; α-ethyl-β-(methylsulfinyl)styrene, (*cis*), 24377-99-9; α-ethyl-β-(methylsulfinyl)styrene (*trans*), 24378-00-5; 1-(methylsulfinyl)-1-(methylmercapto)-2,2-diphenylethylene, 24407-42-9; β-(methylsulfinyl)-β-(methylmercapto)-α-methylstyrene, 24378-02-7; β-(methylsulfinyl)-β-(methylmercapto)-α-ethylstyrene, 24378-03-8; methyl phenethynyl sulfoxide, 24378-04-9; methyl phenethynyl sulfone, 24378-05-0; α-ethoxy-β-(methylsulfinyl)styrene, 24378-06-1.

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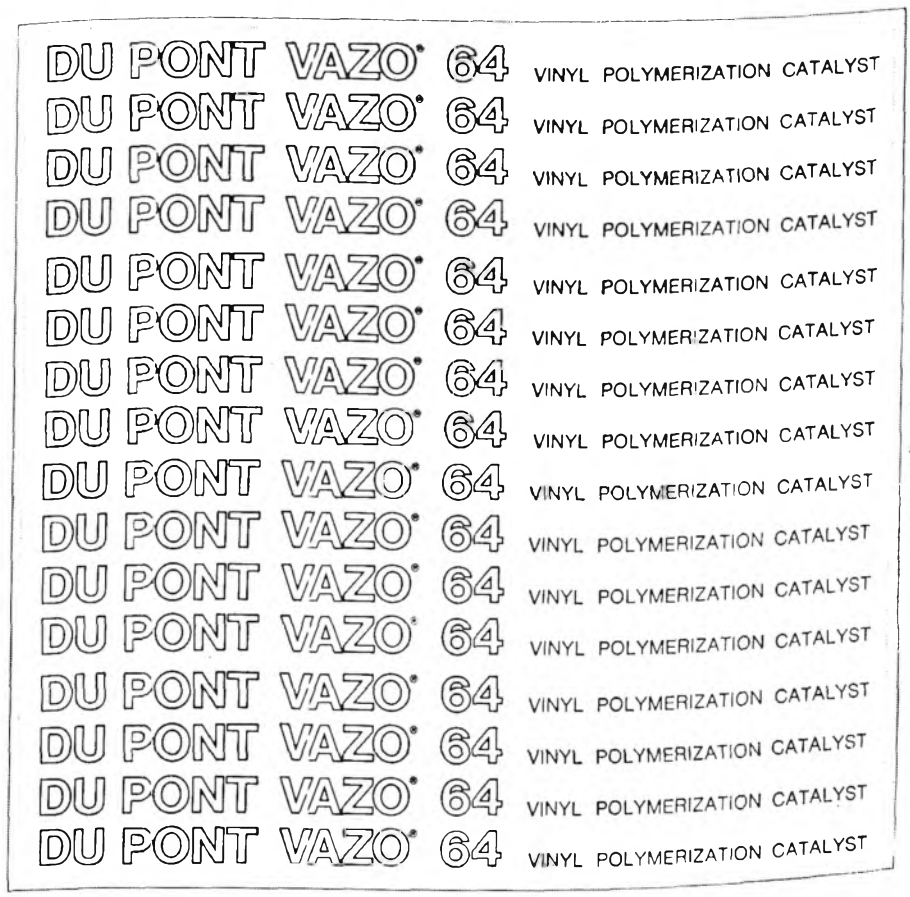

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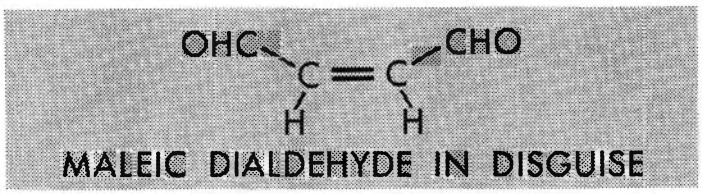

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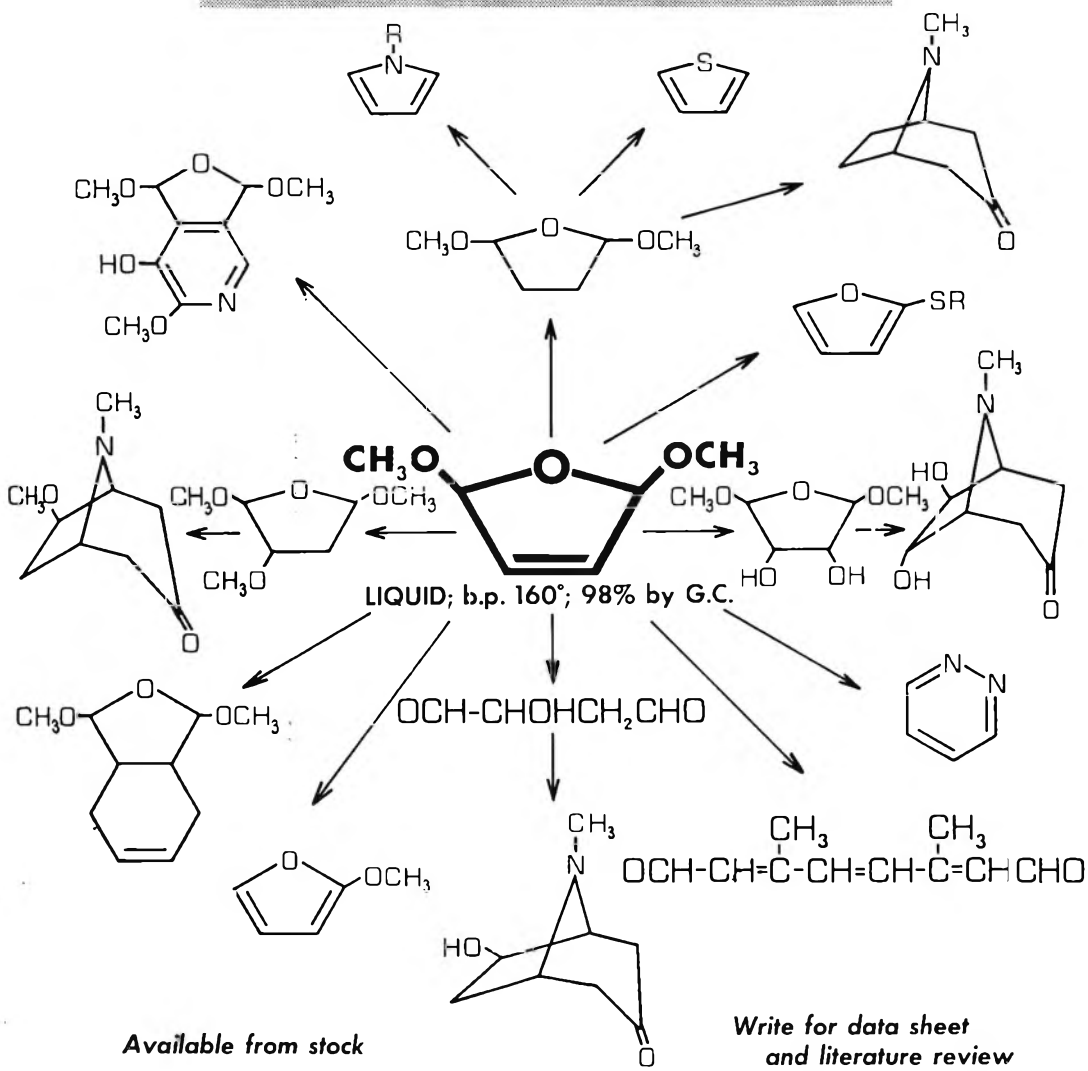

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