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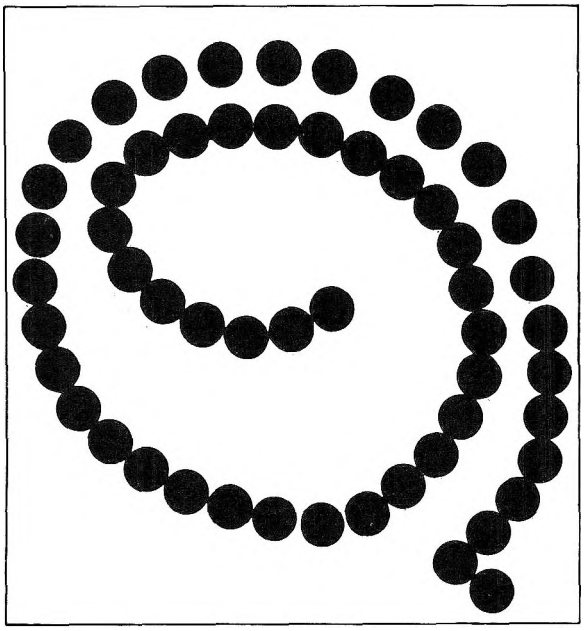

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VOLUME 36, NUMBER 22

NOVEMBER 5, 1971

The Reactions of Grignard Reagents with Norbornene Oxides

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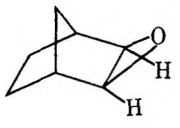
Received March 29, 1971

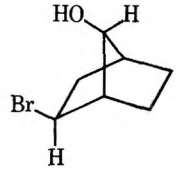
Reaction of phenylmagnesium bromide with *exo*-norbornene oxide (**1**) gave a 3.3:1.0 molar mixture of 7-*syn*-norbornenol to 2-*exo*-phenyl-7-*syn*-norbornanol. Other aryl Grignard reagents behaved similarly. Methylmagnesium iodide reacted with **1** to give a mixture of 7-*syn*-norbornenol, 2-*exo*-methyl-7-*syn*-norbornanol, and 2-*exo*-methyl-7-*anti*-norbornanol. Phenylmagnesium bromide reacted with 2-phenylnorbornene 2,3-*exo*-oxide to give the nonrearranged exo addition product, 3,3-diphenyl-2-*exo*-norbornanol.

Part A

The preparation of norbornene 2,3-*exo*-oxide, or simply norbornene oxide (**1**), was reported initially and simultaneously by Walborsky and Loncrini[1] and Kwart and Vosburgh.[2] Acidic reagents cause facile oxirane ring opening to give rearrangement products. Crandall[3] has shown that acid hydrolysis of **1** gives four isomeric norbornanediols, all products of rearrangement. Reaction with 48% hydrobromic acid gives the bromohydrin, 2-*exo*-bromo-7-*syn*-norbornanol (**2**).[4]

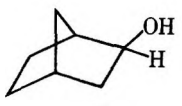


1



2

Reductions of **1** with metal hydrides, principally lithium aluminum hydride ($LiAlH_4$), have been successful. $LiAlH_4$ reduction in ether proceeds very slowly;[5] more polar and higher boiling solvents such as tetrahydrofuran (THF),[5,6] *N*-ethylmorphiline (NEM),[1,5] and THF–diglyme[6] have been employed. The major product from reduction in NEM and THF is *exo*-norbornanol (**3**), with minor amounts of the rearrangement product, 7-norbornanol (**4**), which amounts were dependent on solvent composition and reaction temperature. Recently, a new convenient procedure for the facile reduction of norbornene oxides without rearrangement was developed, utilizing lithium in ethylenediamine.[7] The slower hydride reduction of I may be ascribed to the difficulty accompanying endo nucleophilic attack from the approximate direction of the C_6 endo hydrogen.[8]



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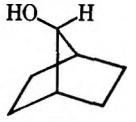
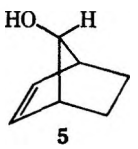


4

In view of the extensive synthetic utility of the Grignard reaction, it is surprising that no report of such a reaction with I has appeared to date. For the purpose of providing a useful synthetic route to various substituted norbornanols, we decided to investigate the addition of various Grignard reagents to **1**.

Results and Discussion

By using a 1.5:1.0 molar ratio of phenylmagnesium bromide to **1**, a 3.3:1.0 mixture (molar) of two products was obtained (glc analysis). The more volatile and more plentiful component was shown to be 7-*syn*-norbornenol (**5**), by nmr analysis and by conversion to the known derivative, 7-*syn*-norbornenyl tosylate.[4a] The less volatile component was identified as 2-*exo*-phenyl-7-*syn*-norbornanol (**6**). Its properties differed from those of 3-*endo*-phenyl-2-*exo*-norbornanol,[9] the product expected from endo attack (trans oxirane open-



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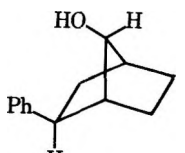


6

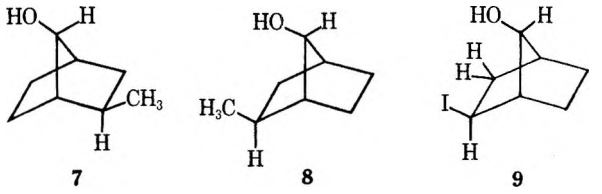
(1) H. M. Walborsky and D. F. Loncrini, *J. Amer. Chem. Soc.*, **76**, 5396 (1954).
(2) H. Kwart and W. G. Vosburgh, *ibid.*, **76**, 5400 (1954).
(3) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).
(4) (a) S. Winstein and E. T. Stafford, *J. Amer. Chem. Soc.*, **79**, 505 (1957); (b) H. M. Walborsky and D. F. Loncrini, *J. Org. Chem.*, **22**, 1117 (1957).
(5) H. Kwart and T. Takeshita, *ibid.*, **28**, 670 (1963).
(6) N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 2927 (1968).
(7) H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **92**, 6914 (1970).
(8) T. G. Traylor, *Accounts Chem. Res.*, **2**, 157 (1969).
(9) D. C. Kleinfelter, T. E. Dye, J. E. Mallory, and E. S. Trent, *J. Org. Chem.*, **32**, 1734 (1967).

ing), and of 3-*exo*-phenyl-2-*exo*-norbornanol,[9] the product expected from unrearranged exo attack (cis oxirane opening).

The reactions of *p*- and *o*-tolylmagnesium bromides with **1** proceeded similarly, giving a product distribution of **5** to 2-*exo*-aryl-7-norbornanol of 3.2:1.0 and 5.7:1.0 (molar), respectively. While all three aryl Grignard reactions gave greater amounts of **5** than of aryl adduct, the availability of norbornene and **1** makes this route an attractive one for such 2-*exo*-aryl-7-*syn*-norbornanols and derivatives. In addition, the reaction provides a simpler route to **5** than previously reported.[4]

Somewhat different results were obtained from the reaction of methylmagnesium iodide with **1**. In eight of nine determinations of product distributions, **5** and two less volatile components, separable by preparative vapor phase chromatography (vpc) were formed. Their elemental analyses and mass spectra ($M\cdot^+$ = 126) indicated them to be isomeric methylnorbornanols. From analysis of their nmr spectra structures **7** and **8** were assigned to the more volatile component (mp 150–151°) and less volatile component (amorphous glassy solid), respectively.

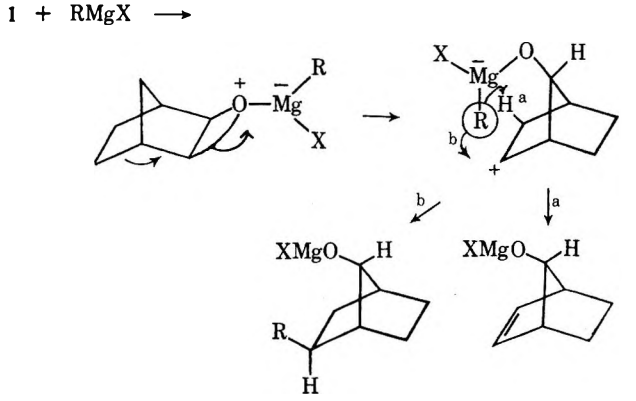
In one of the nine reactions of methylmagnesium iodide with **1**, the iodohydrin, 2-*exo*-iodo-7-*syn*-norbornanol (**9**), was isolated in *ca.* 11% yield.[10]



7 **8** **9**

The products of the reactions of the aryl Grignard reagents with **1** may be rationalized *via* mechanistic Scheme I. This scheme satisfactorily explains the

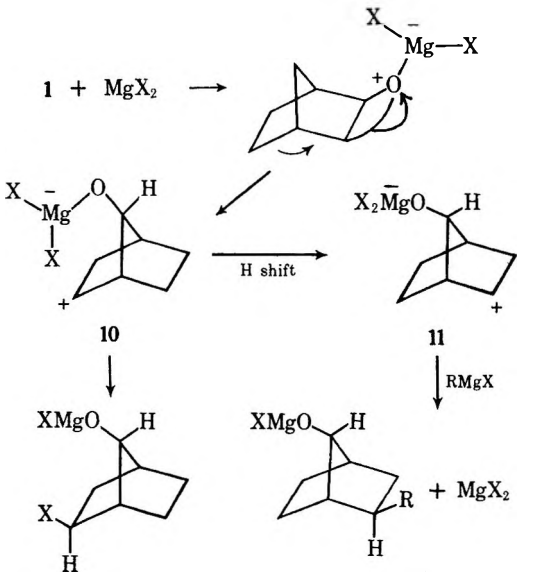
SCHEME I



formation of products **5** and **6**. However, the additional formation of the anti isomer **7** and the iodo addition product **9** requires an extension of this scheme. Reactions of Grignard reagents with epoxides are known to be complicated by the inhomogeneity of solutions due to the equilibrium $2RMgX \rightleftharpoons R_2Mg + MgX_2$.[11]

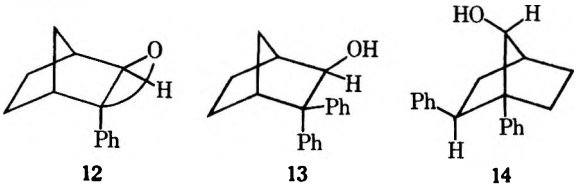
If one assumes that MgX_2 also complexes with **1**,[12] then the formation of the additional products **7** and **9** is understandable (Scheme II). Intermediate **10** may

SCHEME II



add X^- intramolecularly to give **9** or undergo hydride shift to give intermediate **11**, which may then add R to give anti product **2**. The nature of the Grignard reagent is known to be dependent upon the variables of solvent concentration, R group, and halide.[13] Evidently there is sufficient MgI_2 present to compete with RMgI for the oxirane ring complexation in the reaction with the methyl Grignard reagent, but there is insufficient $MgBr_2$ present with the phenyl Grignard reagent or it does not compete favorably with PhMgBr for the oxirane ring complexation. It was felt that use of a bulky Grignard reagent in which the initial complexation of RMgX may be sterically hindered, or in which the reaction of RMgX with the cationic center may be sterically encumbered, might lead to greater halohydrin formation through greater MgX_2 involvement. Reaction of "*tert*-butylmagnesium bromide" with **1** led to a 51% yield of the bromohydrin **2**. This represents a better yield of **2** and a simpler preparative procedure than that previously reported.[4]

One substituted norbornene oxide, 2-phenylnorbornene 2,3-*exo*-oxide (**12**), was treated with phenylmagnesium bromide. The product was 3,3-diphenyl-2-*exo*-norbornanol (**13**), formed *via* cis oxirane ring opening, rather than the rearrangement product, 1-phenyl-2-*exo*-phenyl-7-*syn*-norbornanol (**14**). Structure **13** was assigned from its nmr and ir spectra.



12 **13** **14**

(10) The only difference noted for this reaction was the use of a fresh bottle of methyl iodide; all reactions were carried out under practically identical conditions of time, temperature, work-up, etc.

(11) N. G. Gaylor and E. I. Becker, *Chem. Rev.*, **49**, 413 (1951).

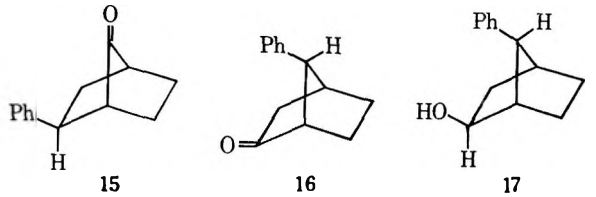
(12) J. K. Crandall (ref 3) reported that $MgBr_2$ reacts with **1** in ether to give minor amounts of **5**, norcamphor, and nortricyclanol; the two major components were probably the syn bromohydrin **2** and its anti isomer. From this latter mixture there was crystallized a compound with mp 72–74°, close to that reported for **2** (mp 75–76°).[4]

(13) R. M. Salinger and H. S. Mosher, *J. Amer. Chem. Soc.*, **86**, 1782 (1964), and references therein; E. C. Ashby, *Quart. Rev., Chem. Soc.*, **21**, 259 (1967).

Rearrangements accompanying reactions of Grignard reagents with epoxides are common,[14] but generally the rearrangement is an initial magnesium halide catalyzed isomerization of the epoxide to an aldehyde or ketone which then reacts with RMgX or R_2Mg. The reactions of phenylmagnesium bromide and methylmagnesium iodide with **1** represent, to our knowledge, the first instances of a Wagner–Meerwein rearrangement and a 1,3-hydride shift accompanying a Grignard addition. It is of interest to note that the reaction of MeMgI with **1** gives the same type rearrangement products as from acid hydrolysis, and that **12** reacts with PhMgBr to give nonrearranged addition product as it does with methanol and other reagents.[15] Evidently it is the Lewis acid nature of the Grignard reagent that is controlling the mode of reaction with **1**.

Part B

Chemical and Spectra Proofs of Structure.—The structure of 2-*exo*-phenyl-7-*syn*-norbornanol (**6**) was confirmed by analysis of its nmr spectrum and by Sarett oxidation[16] to 2-*exo*-phenyl-7-norbornanone (**15**). The three stretching vibrations of 1834 (m), 1771 (s), and 1740 cm^{-1} (w) are consistent with those reported for the carbonyl group of 7-norbornanones.[17] Lithium aluminum hydride reduction of **15** produced the original alcohol **6**. This latter result confirms the exo–syn relationship between the phenyl and hydroxyl groups. The analogous reduction of 7-*syn*-phenyl-2-norbornanone (**16**) gives 7-*syn*-phenyl-2-*exo*-norbornanol (**17**).[18] Hydride attack at the carbonyl group in both **15** and **16** occurs from the side away from the phenyl substituent.



15 **16** **17**

The principal OH stretching vibration of **6** was observed at 3623 cm^{-1} with a barely discernible shoulder of 0.6 relative intensity at *ca.* 3604 cm^{-1}. This contrasts with the single absorption of 3591 cm^{-1} ($\Delta\nu$ = 29 cm^{-1}) reported[19] for its counterpart (**17**). Even if one uses the 3631-cm^{-1} OH band of 2-*exo*-methyl-7-*syn*-norbornanol as the reference-free OH band, **6** definitely experiences weaker and less intramolecular OH---π bonding than **17**.

Whereas **9** and all other secondary phenylnorbornanols previously reported[9,19] display singlets in the phenyl region of their nmr spectra, the spectrum of **6** displays a multiplet centered at δ 7.18. Apparently the phenyl ring is somewhat twisted on edge with respect to the syn hydroxyl, and the proximity of the hydroxy group to the ortho protons causes the resulting magnetic nonequivalence. The previously reported orientational preference of the exo phenyl ring, orthogonal to the eclipsed exo C–H bond,[9] is evidently largely maintained in **6** despite the fact that a different alignment would lead to an energetically favorable OH---π bond. Other distinguishing features of the nmr spectrum of **6** are the 7 anti proton absorption at δ 3.84 (δ 3.90, 7 H of 7-norbornanol) and the 2-endo benzylic proton at δ 2.84 (δ 2.71, 2n H of 2-*exo*-phenylnorbornane[9]).

The 7-proton absorptions do not differ appreciably in the nmr spectra of **7**, **8**, and **4**. The spectrum of **4** shows a broad absorption centered at δ 1.90 (4 H) assignable to the two bridgehead protons, H-1 and H-4, and to the two exo protons, H-2x and H-3x, syn to the hydroxyl group. Snyder and Franzus[20] reported that a syn hydroxyl group deshields exo protons. The spectrum of **7** shows a similar broad absorption centered at δ 1.90 (4 H) assigned to the same protons, but that of **8** shows a downfield absorption at δ 1.97 integrating for only one proton. This δ 1.97 absorption may be assigned to one of the bridgehead protons. The shielding ability of adjacent methyl groups has been observed and commented on by Musher[21] and Eliel.[22] Only the 3-exo proton of **8** can be deshielded by a syn hydroxy group, but the greater shielding ability of the eclipsed 2-methyl easily counteracts this effect. At most then only two protons, the bridgehead protons, should appear downfield; however, only one of the two is observed downfield.

These nmr structural assignments were confirmed by comparison of the nmr dilution curves of **7** and **8** with that of 2-*exo*-cyclohexyl-7-*syn*-norbornanol (**18**), prepared by catalytic hydrogenation of **6**. These curves are shown in Figure 1. The syn alcohols show smaller slopes, $(d\delta/dx)_{x=0}$, in that portion of the plot presumably involving dimer–monomer or oligomer–monomer equilibria.[23] The slopes for **8** and **18** of 28 and 27, respectively, contrast with the value of 57 for the less encumbered hydroxyl of **7**. Oulette[24] has obtained similar results with 2-*exo*-norbornanols with 7-methyl substituents.

The structure of 2-*exo*-iodo-7-*syn*-norbornanol (**9**) was assigned on the basis of the following spectral data. A broad singlet assigned to H-7a appeared at δ 4.17. An eight-line absorption at δ 3.89 was assigned to H-2n. The multiplet spacings, J'[25] of 7.8, 4.2, and 1.2 Hz, may be assigned to coupling of H-2n with H-3n, H-3x, and H-7a, respectively. In the infrared spectrum of **9** OH stretching vibrations

(14) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959); J. D. Morrison, R. L. Atkins, and J. E. Tomaszewski, *Tetrahedron Lett.*, 4635 (1970), and references therein.

(15) T. J. Gerteisen, D. C. Kleinfelter, G. C. Brophy, and S. Sternhell, *Tetrahedron*, in press.

(16) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(17) C. F. H. Allen, T. Davis, D. W. Stewart, and J. A. Van Allen, *J. Org. Chem.*, **20**, 306 (1955); C. F. H. Allen and J. A. Van Allen, *ibid.*, **20**, 323 (1955); P. Wilder, Jr., and A. Winston, *J. Amer. Chem. Soc.*, **78**, 868 (1956); W. R. Hatchard and A. K. Schneider, *ibid.*, **79**, 6261 (1957); P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964); P. G. Gassman and J. L. Marshall, *J. Amer. Chem. Soc.*, **88**, 2822 (1966); E. J. Corey and R. S. Glass, *ibid.*, **89**, 2600 (1967).

(18) J. H. Long, Jr., Ph.D. Thesis, University of Tennessee, 1968.

(19) D. C. Kleinfelter, *J. Org. Chem.*, **32**, 3526 (1967).

(20) E. J. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964).

(21) J. I. Musher, *Mol. Phys.*, **6**, 94 (1963).

(22) E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, No. 17, 741 (1962).

(23) For a discussion of the various effects contributing to the chemical shifts of hydroxyl protons and pertinent references, see J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1965, p 537–547, 816–818.

(24) R. J. Oulette, G. E. Booth, and K. Liptak, *J. Amer. Chem. Soc.*, **87**, 3436 (1965).

(25) Since the 3-proton signals were overlapped by peaks from the remaining methylene hydrogens, the actual coupling constants, J, could not be determined from the spectra. $J' \cong J$ if $\Delta\nu(3x - 3n)$ is large compared to $J_{3x,3n}$.

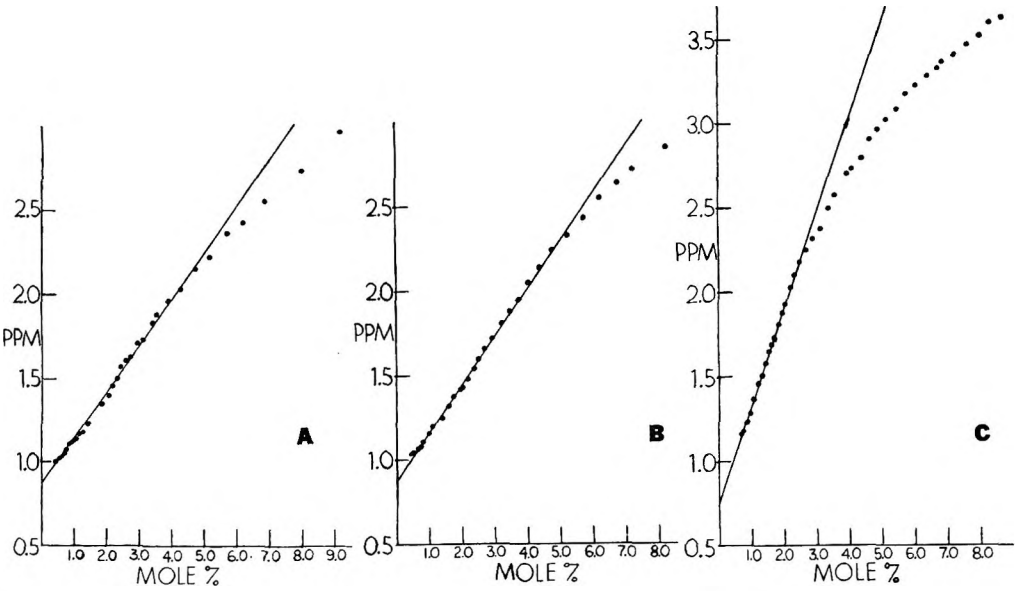


Figure 1.—Plots of chemical shifts *vs.* mole percentages for (a) 2-*exo*-cyclohexyl-7-*syn*-norbornanol (**18**), (b) 2-*exo*-methyl-7-*syn*-norbornanol (**8**), and (c) 2-*exo*-methyl-7-*anti*-norbornanol (**7**).

were observed at 3620 (free) and 3574 cm^{-1} (OH---I bond) with a $\Delta\nu$ of 46 cm^{-1}. Thus the exo-iodo, syn-OH assignments are confirmed.

The nmr spectrum of 3,3-diphenyl-2-*exo*-norbornanol (**13**) showed the following significant absorptions: a broad singlet at δ 4.43 (H-2n), broad singlets at δ 3.07 and 2.20 (H-4 and H-1, respectively), and a broadened doublet (separation *ca.* 10 Hz) at δ 2.10 (H-7s). The ir spectrum showed the OH stretching vibration at 3587 cm^{-1}, corresponding to a $\Delta\nu$ of 33 cm^{-1} with respect to the 3620-cm^{-1} absorption[19] for *exo*-norbornanol. The $\Delta\nu$ for 3-*exo*-phenyl-2-*exo*-norbornanol is 30 cm^{-1}. These spectral data are incompatible with the rearranged product 1-phenyl-2-*exo*-phenyl-7-*syn*-norbornanol (**14**).

Experimental Section

Melting points were determined in soft capillary tubes using a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) and are uncorrected. Infrared spectra for the 3-μ region were recorded on a Perkin-Elmer Model 257 grating spectrometer calibrated against polystyrene standard. A Varian A-60 nmr spectrometer, calibrated with tetramethylsilane (δ = 0) and chloroform (δ = 436.5 cps), was used for the nmr determinations. Chemical shifts are presumed correct to $\pm$0.01 ppm. For the nmr spectra, s = singlet, m = multiplet, b = broad, and exch = exchanges on shaking with D_2O. Relative intensities are given in numbers of protons, *e.g.*, "3 H" denotes a relative intensity of three protons. The mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E recording mass spectrometer (the University of Tennessee, Mr. William Peed, operator), or with a Consolidated Electronics Corp. 21-104 recording mass spectrometer (Phillips Morris Research Laboratoris, Richmond, Va., Dr. Paul H. Chen, operator). Vpc analyses were run on a Varian A90-P3 gas chromatograph equipped with a 6 ft $\times$ 0.25 in. 20% SE-30 on a Chromosorb W column (typical flow rate 50–75 cc min^{-1} of helium, column temperature of 130–185°) or on a Varian A600-D flame ionization detector gas chromatograph equipped with a 5 ft $\times$ $^1/_8$ in. 3% SE-30 on a Chromosorb W column. Preparative scale vpc separations were performed with an Aerograph Autoprep A-700 gas chromatograph equipped with a 20 ft $\times$ $^3/_8$ in. 30% SE-30 on a Chromosorb P column (typical flow rate 100 cc min^{-1} of helium, column temperature of 120–160°). Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn., and by F. B. Strauss Microanalytical Laboratory, Oxford, England.

Unless otherwise specified, all ether and ligroin solutions of products were dried over anhydrous sodium sulfate prior to removal of solvent. Ligroin was distilled over potassium permanganate and had bp 40–55°.

Reaction of Phenylmagnesium Bromide with Norbornene Oxide (1).—To an ether solution of phenylmagnesium bromide, prepared from magnesium turnings (2.0 g, 0.084 g-atom) and bromobenzene (10.7 g, 0.0700 mol), was added an ether solution of **1** (6.60 g, 0.0600 mol), mp 125–126° (lit.[1] mp 125–127°). Reflux was maintaned for 3 hr, water was added, and solvent was removed by flash evaporation with gentle heating from a warm water bath,[26] leaving 7.11 g of light yellow oil. Glc analysis indicated two products in the weight ratio of 2.13:1.00.

A combined distillation and sublimation of 7-*syn*-norbornenol (**5**) *in vacuo* was accomplished by gentle heating. Purification by preparative vpc gave crystalline **5**, mp 79–80°. The *p*-toluenesulfonate, prepared in the usual manner,[27] recrystallized from ether–ligroin gave mp 66–67° (lit.[4a] mp 67–68°). Reduction of **5** with hydrogen and platinum oxide in ethyl acetate gave 7-norbornanol (**4**), mp 148–150° (lit.[28] mp 150–151°). The high-resolution ir spectrum of **4** (CCl_4) showed absorption at 3632 cm^{-1} (OH); that of **5** showed absorption at 3575 cm^{-1} (lit.[29] 3572 cm^{-1}).

Addition of ligroin to the residue left from distillation of **5** affected crystallization of **6**, mp 75–77° from ligroin (*Anal.* Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.16; H, 8.39). The nmr and ir spectra are discussed in the body of the paper. The *p*-toluenesulfonate of **6**, prepared in the usual manner,[27] gave mp 78–79° from ether (*Anal.* Calcd for $C_{20}H_{22}SO_3$: C, 70.16; H, 6.48. Found: C, 69.96; H, 6.47). The weight of **5** and **6**, 7.19 g, represents a yield of 93% (vpc). The molar ratio of **5** to **6** formed was 3.5:1.0; the average for four reactions was 3.3:1.0.

Oxidation of 6 to 2-*exo*-Phenyl-7-norbornanone (15).—To a solution of chromium trioxide (2.0 g, 0.020 mol) in pyridine (20 ml) was added **6** (1.0 g, 0.0053 mol) dissolved in pyridine (20 ml). After stirring for 24 hr at room temperature, the mixture was poured into water and filtered over celite, and the filtrate was extracted with benzene. The benzene solution was washed with water and dried, and the solvent was flash evaporated. A light yellow oil, 0.70 g (69%), of pure (ir, nmr, vpc) **15** was obtained.

Pertinent ir data are listed in the text; nmr (CCl_4) δ 7.11 (5 H, Ar H's), 2.93 (1 H, m, H-2n), 2.3–1.5 (8 H, m, remaining H's).

(26) Caution must be observed at this point to keep the 7-*syn*-norbornenol from escaping by sublimation.

(27) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1180.

(28) S. Winstein, M. Shatavwky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, **77**, 4183 (1955).

(29) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

Reduction of **15** (1.35 g, 0.0140 mol) with lithium aluminum hydride (0.27 g, 0.0070 mol) in ether in the standard manner[30] gave pure **6** (1.14 g, 84.0%) as shown by melting point, ir, and nmr.

Preparation of 2-*exo*-Cyclohexyl-7-*syn*-norbornanol (18).—A mixture of acetic acid (30 ml), 2-*exo*-phenyl-7-*syn*-norbornanol, **6** (1.00 g, 0.00532 mol), and platinum oxide (0.20 g) was hydrogenated iu a Paar apparatus for 10 hr under 45-psi hydrogen pressure. After filtration through Celite, the acetic acid solution was stirred with sodium carbonate solution and extracted with ether, and the ether extracts were washed with sodium carbonate solution. To this dried ether solution was added lithium aluminum hydride (0.75 g) to reduce the acetate that formed during the hydrogenation. Work-up in the usual manner gave **18**, (0.82 g, 80%): mp 75–77°, from ligroin (*Anal.* Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.13; H, 11.28); ir (CCl_4) 3635, 3627 cm^{-1} doublet (OH); nmr (CCl_4, 9.2 mol %) δ 3.86 (1 H, b s, H-7a), 2.96 (1 H, s, exch, OH), 2.2–0.8 (20 remaining H's, m).

Reaction of *p*- and *o*-Tolymagnesium Bromide with 1.—The reactions were carried out in a manner similar to that used for the preparation of **6**. For the *p*-tolyl Grignard reagent a 3.0:1.0 molar ratio of **5** to *p*-tolyl adduct was formed. The *p*-tolyl analog of **6** had mp 70–71° from ligroin (*Anal.* Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.97; H, 8.86); ir (CCl_4) 3624, 3604 cm^{-1} sh (intensity ratio 1.22:1.00); nmr similar to **6**. For the *o*-tolyl Grignard reagent a 5.7:1.0 molar ratio of **5** to *o*-tolyl adduct was formed. The *o*-tolyl analog of **6**, a light yellow oil, was converted to its *p*-toluenesulfonate derivative in the usual manner,[27] which gave mp 110–112° from ether–ligroin (*Anal.* Calcd for $C_{21}H_{24}SO_3$: C, 70.78; H, 6.74. Found: C, 70.64; H, 6.72). For the alcohol, ir (CCl_4) showed 3621, 3604 cm^{-1} sh (intensity ratio 1.24:1.00); nmr similar to **6**.

Reaction of Methylmagnesium Iodide with 1.—The reaction was carried out in a manner similar to that used for the preparation of **6**. Using iodomethane (19.6 g, 0.140 mol), magnesium turnings (7.25 g, 0.300 g-atom), and **1** (10.0 g, 0.0909 mol), there was obtained 7.96 g of pale yellow oil. Vpc analysis gave 25.3% (molar) **5**, 33.6% **7**, and 41.5% **8**. The average for three preparations was 28.0% **5**, 31.9% **7**, and 40.1% **8**. The per cent yield based on the three products was 71.6%; the average for three preparations was 74.1%. Gentle distillation *in vacuo* with trapping in a Dry Ice–acetone bath separated most of **5** from the methylnorbornanols. Preparative vpc gave pure **8**, a white crystalline solid, mp 150–151° from ligroin, and **7**, a clear, glassy, amorphous solid of low melting point (*Anal.* Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found (for **8**): C, 75.90; H, 10.92. Found (for **7**): C, 75.90; H, 11.08). In their ir spectra (CCl_4) both absorbed at 3631 cm^{-1}; the significant nmr spectral data are discussed in the text.

(30) W. G. Brown, *Org. React.*, **6**, 469 (1951).

Isolation of 2-*exo*-Iodo-7-*syn*-norbornanol (9).—In one of the nine reactions of methylmagnesium iodide in which there were reacted iodomethane (29.8 g, 0.210 mol), magnesium turnings (10.1 g, 0.414 g-atom), and **1** (15.0 g, 0.136 mol) in the usual manner, removal of the ether solvent in the work-up left some white solid and oily material. Addition of ligroin dissolved the oil after which the solid was filtered to give **9** (3.63 g, 11.3%): mp 72–73.5° from ligroin (*Anal.* Calcd for $C_7H_{11}IO$: C, 35.29; H, 4.62. Found: C, 35.04; H, 4.58); ir (CCl_4) 3620 (ν_f), 3574 cm^{-1} (ν_b), $\Delta\nu$ 46 cm^{-1} (intensity ratio = 1.0:1.0); pertinent nmr assignments in text. Vpc analysis of the filtrate gave 29.5% **5**, 10.0% **7**, and 49.2% **8**, relative to total moles of the four products.

Reaction of *tert*-Butylmagneium Bromide with 1.—The reaction was carried out in a manner similar to that used for the preparation of **6**. From *tert*-butyl bromide (19.0 g, 0.139 mol), magnesium turnings (4.0 g, 0.16 g-atom), and **1** (9.20 g, 0.0836 mol) there was obtained 13.44 g of colorless oil. Addition of ligroin with stirring caused precipitation of white solid. Filtration in the cold gave 8.06 g (50.5%) of 2-*exo*-bromo-7-*syn*-norbornanol, mp 75–76° (lit.[4a] mp 75–76°). The nmr spectrum of the ligroin-evaporated filtrate showed that a small amount of 7-*syn*-norbornenol was present. No attempt was made to determine further the composition of this filtrate (5.38 g). For the bromohydrin, ir (CCl_4) showed 3621 sh (ν_f), 3577 cm^{-1} (ν_b), $\Delta\nu$ 44 cm^{-1} (intensity ratio = 1.0:2.2); nmr (CCl_4) δ 4.01 (1 H, s broad, H-7a), 3.95 (1 H, m, H-2n), 2.50 (1 H, s, exch OH), 2.8–0.85 (8 H, remaining H's).

Reaction of Phenylmagnesium Bromide with 2-Phenylnorbornene 2,3-*exo*-Oxide (12).—The reaction was carried out in a manner similar to that used for the preparation of **6**. Using bromobenzene (9.42 g, 0.0600 mol), magnesium turnings (1.92 g, 0.0800 g-atom), and **12** (5.00 g, 0.0270 mol), there was obtained *ca.* 6.0 g of light yellow oil. Chromatography over alumina, using ligroin eluent, removed the biphenyl and other impurities. Elution with ether gave 5.00 g (70.4%) of alcohol **13**, mp 75.5–77.0° from ligroin (*Anal.* Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.08; H, 7.66). The ir and nmr spectra are discussed in the text.

Registry No.—**1**, 3146-39-2; **2**, 31337-62-9; **5**, 13118-70-2; **6**, 31337-64-1; **6** *p*-toluenesulfonate, 31337-65-2; **6** *p*-tolyl analog, 31337-66-3; **6** *o*-tolyl analog *p*-toluenesulfonate, 31337-67-4; **7**, 31337-68-5; **8**, 31337-69-6; **9**, 31337-70-9; **12**, 31337-71-0; **13**, 31337-72-1; **15**, 31337-73-2; **18**, 31337-74-3; phenylmagnesium bromide, 100-58-3; *p*-tolylmagnesium bromide, 4294-57-9; *o*-tolylmagnesium bromide, 932-31-0; methylmagnesium iodide, 917-64-6; *tert*-butylmagnesium bromide, 2259-30-5.

Preparation of Some 7,7-Dimethyl-19-nor Steroids by Total Synthesis. Structure Determination by X-Ray Diffraction

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Application of the Torgov–Smith scheme for steroid total synthesis to 6-methoxy-3,3-dimethyl-1-tetralone, whose preparation is described, afforded 7,7-dimethylestradiol 3-methyl ether. This was converted to the 19-nortestosterone analog. X-Ray crystallographic analysis of the latter as the 17-(*p*-bromo)benzoate revealed the compound to have the 8α,14β configuration. An explanation is advanced to rationalize this finding.

In search for hormonal agents with increased potency, fewer side effects, and possible splits in activity, steroid analogs methylated in virtually every accessible position have been prepared.[1] Some such modifications, for example, the compounds methylated in the 6β[2] and 7α[3] positions, have in fact led to biologically interesting agents.

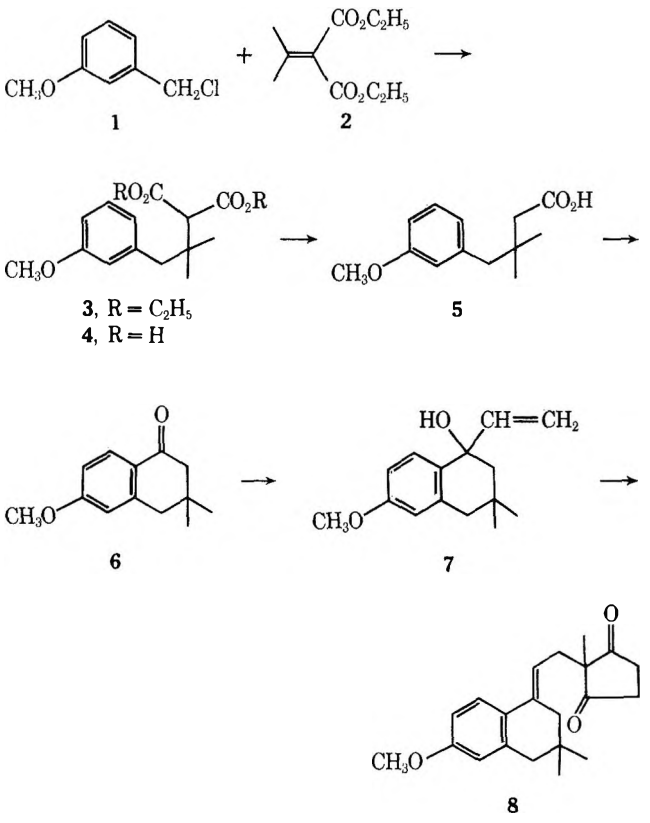
Due in part to difficulties in accessibility, many fewer geminally dimethylated compounds have been examined. The 4,4-dimethyl steroids, prepared by exhaustive methylation of conjugated 3-en-4-ones,[4] and the 7,7-dimethyl compounds prepared by the ingenious scheme of Julia[5] are the best studied examples in this series.

Since the 7α-methyl-19-nor steroids are some of the most potent known agents,[3] we wished to ascertain the effect of adding an additional methyl group in the 7β position of such a molecule. The previously employed scheme for the preparation of the corresponding 19-methyl counterpart[5] proceeds through the 3,5-cyclo steroids; since these are but difficulty accessible in the 19-nor series, we chose to approach our goal by total synthesis. In particular, we chose the versatile and relatively short Torgov–Smith synthesis.[6,7]

The key intermediate, tetralone (**6**), was obtained as shown in Scheme I. Conjugate addition of *m*-methoxybenzylmagnesium chloride to diethyl isopropylidenemalonate proceeded in an average yield of 55%. Neither inverse addition nor the presence of copper salt had any great influence on this yield. Saponification afforded the corresponding dicarboxylic acid. This last was decarboxylated and the oily product cyclized (phosphorus pentachloride–stannic chloride) without prior purification to give the desired bicyclic intermediate.

Reaction of **6** with the vinyl Grignard reagent gave the corresponding alcohol as an oil; attempts to purify this chromatographically led to extensive decomposition. Reaction of the crude alcohol with 2-methylcyclopentane-1,3-dione in the presence of a trace of base[8] completed the buildup of the carbon skeleton to afford **8**.

SCHEME I



Initial attempts at cyclization with *p*-toluenesulfonic acid in benzene gave only isomerization of the styrene double bond, **9**. It was necessary to resort to ethanolic hydrogen chloride to effect the ring closure. The exposure time to acid in this reaction proved critical; in our hands 10 min proved optimum. We further were not able to scale up this reaction beyond 5–10 g. It is of note, too, that the structure of the product represents a deviation from the Torgov scheme; whereas in the previous work there is present an extended conjugated system (**11**), in the dimethyl series, **10**, one double bond is conjugated with the aromatic ring while the other has moved into conjugation with the 17 ketone. This, as we will see, has some important stereochemical consequences.

Catalytic reduction followed by treatment of the product with sodium borohydride led cleanly to the 17 alcohol **13**. Attempted Birch reduction in the absence of added alcohol failed to go in this case, again in con-

(1) E. Tororomanoff, *Bull. Soc. Chim. Fr.*, 888 (1960); P. D. Klimstra and F. B. Colton in "Contraception: The Chemical Control of Fertility," D. Lednicer, Ed., Marcel Dekker, New York, N. Y., 1969.

(2) H. J. Ringold, E. Batres, and G. Rosencrantz, *J. Org. Chem.*, **22**, 99 (1957); G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957); J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *J. Amer. Chem. Soc.*, **80**, 2964 (1958).

(3) J. A. Campbell, S. C. Lyster, G. W. Duncan, and J. C. Babcock, *Steroids*, **1**, 317 (1963).

(4) See, for example, F. Gautschi and K. Bloch, *J. Biol. Chem.*, **233**, 1343 (1958).

(5) S. Julia, C. Neuville, and M. Davis, *Bull. Soc. Chim. Fr.*, 297 (1960).

(6) S. N. Ananchenko and I. V. Torgov, *Dokl. Akad. Nauk. SSSR*, **127**, 533 (1959).

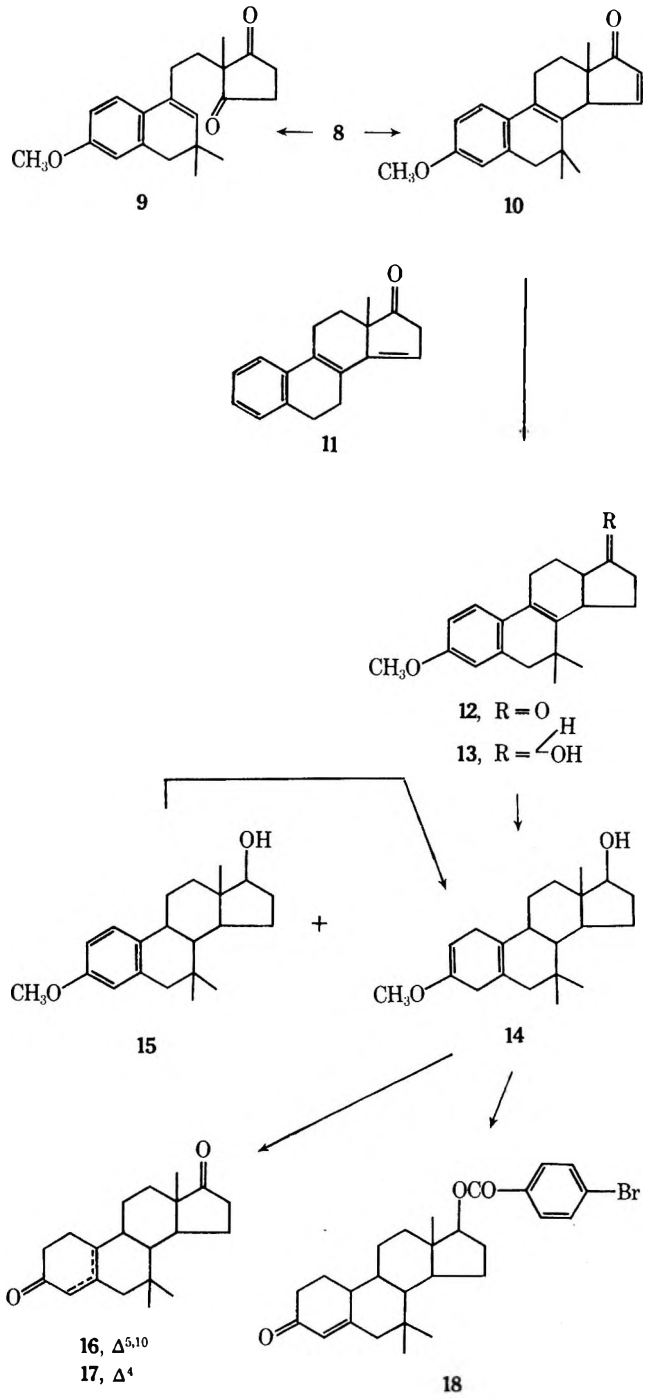
(7) G. A. Hughes and H. Smith, *Chem. Ind. (London)*, 1022 (1960).

(8) For an interesting discussion of the mechanism of this reaction, see C. H. Kuo, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **33**, 3126 (1968).

trast to previous work. Reaction in the presence of *tert*-butyl alcohol invariably produced mixtures of the aromatic compound **15** and the product of overreduction **14**. The former could be converted cleanly to the enol ether by reexposure to the conditions of the Birch reduction.

Hydrolysis of the enol ether proved very slow. Thus, exposure to mineral acid for 18 hr still gave a mixture of the conjugated and unconjugated enones. Since this mixture proved essentially inseparable, it was oxidized with Jones reagent to the diones. This could now be separated to afford **16** and **17** (Scheme II).

SCHEME II



The observed spontaneous shift of the double bond during cyclization casts some doubt on the stereochemistry at the 14 position. Though it is well known that

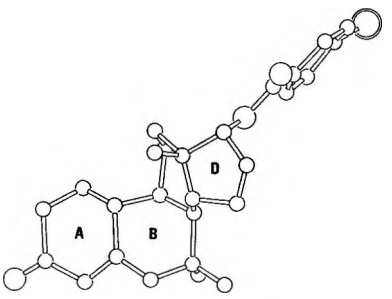


Figure 1.—Drawing, from X-ray results, of one of the symmetry independent molecules of **18**. Drawing is in projection down the *b* axis of the crystal.

perhydroindanes prefer the cis ring junction, molecular models of **10** suggest that the additional methyl groups at 7 may introduce new factors. We turned first to the nmr spectra of these compounds in an effort to clarify the stereochemistry. We had hoped to be able to assign the methyl resonance peaks to individual methyl groups and thus learn something of their environments. As Table I shows, however, these peaks fail to show the type of behavior, in going from compound to compound, to allow an *a priori* assignment.

TABLE I
NMR CHEMICAL SHIFTS OF METHYL GROUPS

Compd	Methyl group resonance, Hz		
8	56	56	70
9	58	58	68
10	63	70	70
12	58	58	67
13	51	55	62
14	53	62	62
15	57	59	59

Since these compounds are, further, too far removed from natural steroids for proof of structure by intraconversion to a known compound, we resorted to X-ray diffraction for determination of stereochemistry. To this end, the enol ether **14** was first treated with 1 equiv of butyllithium. This was then followed by *p*-bromobenzoyl bromide and the product subjected to hydrolysis. Preparative tlc afforded a sample of **18** which on careful crystallization gave a single crystal suitable for the structural work.

X-Ray Diffraction Study.—A three-dimensional X-ray diffraction analysis was carried out using the heavy atom method to obtain a trial structure. Figure 1 shows the conformation and configuration of one of the two symmetry-independent molecules; the other molecule is identical in configuration and very similar in conformation. The configuration at both B–C and C–D ring fusions is cis; these are anti to each other, giving rise to a folding of the molecule at C ring fusions, as shown in Figure 1. The degree of folding may be estimated by calculating angles between the "best" planes through each of the rings in the steroid portion of the molecule. These calculations indicate that the C ring makes angles of about 60, 76, and 45° with A, B, and D rings, respectively. In contrast, the A–B, A–D, and B–D angles are about 16, 18, and 33° (Table II).

The B and C rings have chair conformation and the D ring has four atoms approximately planar and the fifth atom, carbon 17, about 0.5 Å out of this plane. In the A ring, constrained by the double bonds, five of

TABLE II
BOND ANGLES (IN DEGREES) AND STANDARD DEVIATIONS (IN PARENTHESES)

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(2)	C(1)	C(10)	108 (3)	C(2′)	C(1′)	C(10′)	112 (3)
C(1)	C(2)	C(3)	113 (4)	C(1′)	C(2′)	C(3′)	111 (3)
C(2)	C(3)	O(1)	117 (5)	C(2′)	C(3′)	O(1′)	128 (5)
C(2)	C(3)	C(4)	117 (4)	C(2′)	C(3′)	C(4′)	122 (4)
O(1)	C(3)	C(4)	125 (5)	O(1′)	C(3′)	C(4′)	108 (4)
C(3)	C(4)	C(5)	118 (4)	C(3′)	C(4′)	C(5′)	114 (4)
C(4)	C(5)	C(6)	114 (4)	C(4′)	C(5′)	C(6′)	125 (4)
C(4)	C(5)	C(10)	123 (4)	C(4′)	C(5′)	C(10′)	129 (4)
C(6)	C(5)	C(10)	122 (3)	C(6′)	C(5′)	C(10′)	107 (3)
C(5)	C(6)	C(7)	111 (3)	C(5′)	C(6′)	C(7′)	116 (3)
C(6)	C(7)	C(8)	108 (3)	C(6′)	C(7′)	C(8′)	112 (3)
C(6)	C(7)	C(19)	107 (3)	C(6′)	C(7′)	C(19′)	103 (3)
C(6)	C(7)	C(20)	111 (3)	C(6′)	C(7′)	C(20′)	111 (3)
C(8)	C(7)	C(19)	112 (3)	C(8′)	C(7′)	C(19′)	114 (3)
C(8)	C(7)	C(20)	108 (3)	C(8′)	C(7′)	C(20′)	111 (3)
C(19)	C(7)	C(20)	110 (3)	C(19′)	C(7′)	C(20′)	107 (3)
C(7)	C(8)	C(9)	107 (3)	C(7′)	C(8′)	C(9′)	105 (2)
C(7)	C(8)	C(14)	112 (3)	C(7′)	C(8′)	C(14′)	113 (3)
C(9)	C(8)	C(14)	114 (3)	C(9′)	C(8′)	C(14′)	116 (3)
C(8)	C(9)	C(10)	114 (3)	C(8′)	C(9′)	C(10′)	114 (2)
C(8)	C(9)	C(11)	105 (3)	C(8′)	C(9′)	C(11′)	107 (2)
C(10)	C(9)	C(11)	106 (3)	C(10′)	C(9′)	C(11′)	112 (3)
C(1)	C(10)	C(5)	113 (3)	C(1′)	C(10′)	C(5′)	106 (3)
C(1)	C(10)	C(9)	109 (3)	C(1′)	C(10′)	C(9′)	111 (3)
C(5)	C(10)	C(9)	100 (3)	C(5′)	C(10′)	C(9′)	114 (3)
C(9)	C(11)	C(12)	112 (3)	C(9′)	C(11′)	C(12′)	110 (2)
C(11)	C(12)	C(13)	110 (3)	C(11′)	C(12′)	C(13′)	105 (3)
C(12)	C(13)	C(14)	118 (3)	C(12′)	C(13′)	C(14′)	122 (3)
C(12)	C(13)	C(17)	117 (3)	C(12′)	C(13′)	C(17′)	116 (3)
C(12)	C(13)	C(18)	105 (3)	C(12′)	C(13′)	C(18′)	99 (3)
C(14)	C(13)	C(17)	108 (3)	C(14′)	C(13′)	C(17′)	106 (3)
C(14)	C(13)	C(18)	109 (3)	C(14′)	C(13′)	C(18′)	111 (3)
C(17)	C(13)	C(18)	99 (3)	C(17′)	C(13′)	C(18′)	101 (3)
C(8)	C(14)	C(13)	116 (3)	C(8′)	C(14′)	C(13′)	112 (3)
C(8)	C(14)	C(15)	112 (3)	C(8′)	C(14′)	C(15′)	111 (3)
C(13)	C(14)	C(15)	103 (3)	C(13′)	C(14′)	C(15′)	100 (3)
C(14)	C(15)	C(16)	110 (3)	C(14′)	C(15′)	C(16′)	112 (3)
C(15)	C(16)	C(17)	106 (3)	C(15′)	C(16′)	C(17′)	101 (3)
C(13)	C(17)	C(16)	104 (3)	C(13′)	C(17′)	C(16′)	109 (3)
C(13)	C(17)	O(2)	101 (3)	C(13′)	C(17′)	O(2′)	102 (3)
C(16)	C(17)	O(2)	113 (3)	C(16′)	C(17′)	O(2′)	109 (3)
C(17)	O(2)	C(21)	109 (3)	C(17′)	O(2′)	C(21′)	112 (3)
O(2)	C(21)	O(3)	124 (4)	O(2′)	C(21′)	O(3′)	125 (4)
O(2)	C(21)	C(22)	107 (3)	O(2′)	C(21′)	C(22′)	108 (3)
O(3)	C(21)	C(22)	128 (4)	O(3′)	C(21′)	C(22′)	127 (4)
C(21)	C(22)	C(23)	109 (3)	C(21′)	C(22′)	C(23′)	104 (3)
C(21)	C(22)	C(27)	128 (3)	C(21′)	C(22′)	C(27′)	127 (3)
C(23)	C(22)	C(27)	123 (3)	C(23′)	C(22′)	C(27′)	130 (3)
C(22)	C(23)	C(24)	115 (3)	C(22′)	C(23′)	C(24′)	103 (3)
C(23)	C(24)	C(25)	119 (3)	C(23′)	C(24′)	C(25′)	126 (3)
Br(1)	C(25)	C(24)	114 (3)	Br(2)	C(25′)	C(24′)	116 (3)
Br(1)	C(25)	C(26)	122 (3)	Br(2)	C(25′)	C(26′)	123 (3)
C(24)	C(25)	C(26)	121 (3)	C(24′)	C(25′)	C(26′)	121 (4)
C(25)	C(26)	C(27)	121 (3)	C(25′)	C(26′)	C(27′)	118 (3)
C(22)	C(27)	C(26)	119 (3)	C(22′)	C(27′)	C(26′)	121 (3)

the ring atoms are roughly in a plane and carbon 1 is about 0.7 Å out of this plane.

Even considering the rather high standard deviations in this structure determination, there is little doubt that O(1) is a carbonyl oxygen and that there is also a double bond between C(4) and C(5). Bond lengths (Table III) were observed to be 1.22 and 1.24 Å between C(3) and O(1) in the two molecules and 1.39 and 1.40 Å between C(4) and C(5). In addition, plane calculations (Table IV) show that within experimental error the appropriate area is planar in each molecule.

Discussion

In its many applications to date, the Torgov–Smith scheme for the total synthesis of steroids has been notable for the degree of stereochemical control; products with unnatural configuration, if present, are usually by-products.[9] The present deviation from that stereochemistry thus deserves some comment.

In the usual course of events, the product of cyclization of ring C gives a conjugated diene **11**, in which

(9) T. B. Windholz, R. D. Brown, and A. A. Patchett, *Steroids*, **6**, 409 (1965).

TABLE III
BOND LENGTHS (Å) AND STANDARD DEVIATIONS (IN PARENTHESES)

Atom	Atom	Distance	Atom	Atom	Distance
Br(2)	C(25′)	1.89 (0.04)	Br(1)	C(25)	1.85 (0.03)
C(1′)	C(2′)	1.54 (0.05)	C(1)	C(2)	1.49 (0.06)
C(1′)	C(10′)	1.56 (0.05)	C(1)	C(10)	1.55 (0.06)
C(2′)	C(3′)	1.49 (0.06)	C(2)	C(3)	1.68 (0.07)
C(3′)	O(1′)	1.22 (0.05)	C(3)	O(1)	1.21 (0.06)
C(3′)	C(4′)	1.47 (0.07)	C(3)	C(4)	1.52 (0.07)
C(4′)	C(5′)	1.39 (0.05)	C(4)	C(5)	1.40 (0.05)
C(5′)	C(6′)	1.72 (0.05)	C(5)	C(6)	1.48 (0.05)
C(5′)	C(10′)	1.63 (0.05)	C(5)	C(10)	1.66 (0.05)
C(6′)	C(7′)	1.52 (0.05)	C(6)	C(7)	1.54 (0.05)
C(7′)	C(8′)	1.53 (0.04)	C(7)	C(8)	1.66 (0.04)
C(7′)	C(19′)	1.55 (0.05)	C(7)	C(19)	1.48 (0.05)
C(7′)	C(20′)	1.72 (0.05)	C(7)	C(20)	1.58 (0.05)
C(8′)	C(9′)	1.57 (0.04)	C(8)	C(9)	1.51 (0.05)
C(8′)	C(14′)	1.49 (0.04)	C(8)	C(14)	1.62 (0.04)
C(9′)	C(10′)	1.54 (0.05)	C(9)	C(10)	1.60 (0.05)
C(9′)	C(11′)	1.55 (0.04)	C(9)	C(11)	1.53 (0.04)
C(11′)	C(12′)	1.71 (0.04)	C(11)	C(12)	1.57 (0.04)
C(12′)	C(13′)	1.64 (0.05)	C(12)	C(13)	1.64 (0.05)
C(13′)	C(14′)	1.64 (0.05)	C(13)	C(14)	1.44 (0.05)
C(13′)	C(17′)	1.56 (0.05)	C(13)	C(17)	1.63 (0.05)
C(13′)	C(18′)	1.59 (0.05)	C(13)	C(18)	1.68 (0.05)
C(14′)	C(15′)	1.52 (0.05)	C(14)	C(15)	1.62 (0.05)
C(15′)	C(16′)	1.63 (0.05)	C(15)	C(16)	1.46 (0.04)
C(16′)	C(17′)	1.43 (0.05)	C(16)	C(17)	1.46 (0.05)
C(17′)	O(2′)	1.53 (0.04)	C(17)	O(2)	1.61 (0.04)
O(2′)	C(21′)	1.43 (0.04)	O(2)	C(21)	1.39 (0.04)
C(21′)	O(3′)	1.17 (0.04)	C(21)	O(3)	1.12 (0.05)
C(21′)	C(22′)	1.60 (0.05)	C(21)	C(22)	1.54 (0.05)
C(22′)	C(23′)	1.51 (0.05)	C(22)	C(23)	1.49 (0.05)
C(22′)	C(27′)	1.41 (0.05)	C(22)	C(27)	1.38 (0.05)
C(23′)	C(24′)	1.44 (0.05)	C(23)	C(24)	1.48 (0.05)
C(24′)	C(25′)	1.51 (0.05)	C(24)	C(25)	1.39 (0.05)
C(25′)	C(26′)	1.34 (0.05)	C(25)	C(26)	1.43 (0.05)
C(26′)	C(27′)	1.33 (0.05)	C(26)	C(27)	1.38 (0.05)

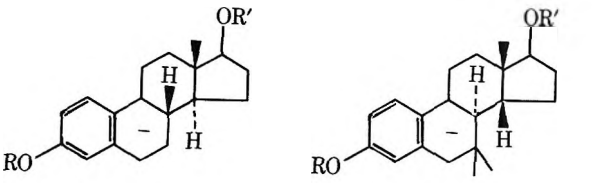
TABLE IV
DEVIATIONS (Å) FROM LEAST-SQUARES PLANES THROUGH THE CONJUGATED DOUBLE BONDS PORTION OF THE MOLECULE[a]

	Molecule 1	Molecule 2
	C(2) 0.10	C(2′) 0.10
	C(3) −0.03	C(3′) −0.09
	O(1) 0.03	O(1′) 0.04
	C(4) −0.11	C(4′) −0.05
	C(5) −0.06	C(5′) −0.02
	C(6) 0.13	C(6′) 0.08
	C(10) −0.07	C(10′) −0.07
cos (*a*)	0.200	0.222
cos (*b*)	0.927	−0.929
cos (*c*)	−0.317	0.295
d_{origin}	1.83 Å	4.17 Å

[a] Direction cosines are with respect to the real cell axes.

C-14 is trigonal. Molecular models reveal that in the present series such a structure involves considerable interaction between the geminal dimethyl groups at 7 and the proton at C-15. The shift of the double bond to 15 relieves this strain by introducing a "fold" at the C–D ring junction. Since both double bonds of the new system 10 are conjugated, little of the delocalizing energy present in **11** is lost. It is apparent too that the normal preference for cis five–six ring fusions asserts itself. It is not, however, at present clear why the borohydride reduction of the 17 ketone goes so cleanly to the α alcohol.

The stereochemistry of the Birch reduction of enones has been clearly delineated.[10] Though considerable work has been carried out on the steric course of the reduction of styrenoid systems,[11] this reaction is not nearly as well understood. Precedent suggests, however, that the predominant product will be that derived from entry of the first proton trans to that present at the proximate saturated carbon atom. In the normal course of events this affords an intermediate such as i. In the present series this proton will add instead from the α side to give the intermediate ii; this accounts for the observed configuration at C-8, in our final product.



i ii

It was proposed some time ago that the direction of addition of the second proton is controlled by kinetic rather than thermodynamic factors.[12] That is, the proton will add from the less hindered side. In the case of intermediate i, this leads to the observed 9α product, an interesting case where the kinetic and thermodynamic predictions coincide. In the 7,7-dimethyl series, however, the less hindered side of the molecule is also the α side; in this case, however, the product of kinetic addition will be the less stable cis B–C ring fusion. Again, this accords with the observed stereochemistry.

In sum then, the fact that C-14 assumed the β configuration at an early stage in the synthesis caused three additional chiral centers to go awry. This finding points up the key importance of the circumstance that the Torgov–Smith scheme leads initially to a trigonal center at C-14; the subsequent catalytic reduction allows the introduction of a proton at 14α, which in turn leads to the natural configuration for the remaining centers.

Experimental Section[13]

Synthesis. Diethyl (*m*-Methoxy-α,α-dimethylphenethyl)malonate (3).—A solution of 13.3 g (0.085 mol) of *m*-methoxybenzyl chloride in 100 ml of ether was added dropwise for 1.5 hr to 2.10 g (0.088 g-atom) of magnesium. The mixture was cooled in ice and treated with 12.0 g of diethyl isopropylidenemalonate[14] in 100 ml of ether. Following 16 hr standing at room temperature, the mixture was cooled in ice and treated with 50 ml of 2.5 *N* hydrochloric acid. The organic layer was washed with water and brine and taken to dryness. The residual oil was distilled at 0.55 mm to give, after some forerun, 14.35 g (52.5%) of the ester, bp 154–163°, largely 161–163°.

(*m*-Methoxy-α,α-dimethylphenethyl)malonic Acid (4).—A solution of 14.14 g (0.044 mol) of the ester and 30 ml of 50% sodium hydroxide in 170 ml of methanol was heated at reflux overnight. The bulk of the solvent was removed *in vacuo* and the residue dissolved in water. The solution was washed with ether and

(10) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).

(11) See, for example, P. W. Rabideau and R. G. Harvey, *J. Org. Chem.*, **35**, 25 (1970); U. R. Ghatak, N. R. Chatterjee, A. K. Banerjee, J. Chakravarty, and R. E. Moore, *J. Org. Chem.*, **34**, 3739 (1969), and references therein.

(12) H. E. Zimmerman, *J. Amer. Chem. Soc.*, **78**, 1168 (1956).

(13) All melting points are uncorrected and reported as obtained on a Thomas-Hoover capillary melting point apparatus. Nmr spectra obtained in deuteriochloroform on a Varian A-60A spectrometer. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Co. for elemental and spectral determinations.

(14) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **60**, 2644 (1930).

then acidified. The precipitated oil was extracted with ether, and this solution washed with brine and taken to dryness. The residue was recrystallized from ether–carbon tetrachloride to afford 7.70 g (66%) of acid, mp 127–132°.

The analytical sample from an earlier run melted at 132–135°; nmr complex aromatic region (4 H) and 2 exchangeable H, singlets at δ 3.8 (3 H), 3.3 (1 H), 2.9 (2 H), 1.15 (6 H). *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81; neut equiv, 266, 133. Found: C, 62.97; H, 6.87; neut equiv, 278, 139.

3,4-Dihydro-6-methoxy-3,3-dimethyl-1(2*H*)-naphthalenone (6).—The malonic acid (9.22 g, 0.034 mol) was heated in a flask immersed in an oil bath at 175–180° until effervescence had completely stopped (40 min). The monoacid was obtained as 7.46 g of viscous oil: nmr complex region δ 6.6–7.4 (4 H), singlets at δ 3.8 (3 H), 2.68 (2 H), 2.25 (2 H), 1.08 (6 H).

Phosphorus pentachloride (7.05 g, 0.034 mol) was added to a solution of the decarboxylation product in 100 ml of benzene. The mixture was heated at reflux for 1 hr and then cooled in ice. Stannic chloride (8.75 g, 0.034-mol) was added and the dark solution stirred under reflux for 1.5 hr. The mixture was cooled in ice and treated with 50 ml of 2.5 *N* hydrochloric acid. The organic layer was separated, washed with water and brine, and taken to dryness. The residue was chromatographed over 700 ml of Florisil[15] (elution with 2% acetone, Skellysolve B).[16] The crystalline fractions were combined and recrystallized from Skellysolve B to give 4.96 g (71.5%) of solid, mp 40–42°. *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.39; H, 7.98.

1,2,3,4-Tetrahydro-6-methoxy-3,3-dimethyl-1-vinyl-1-naphthol (7).—A solution of 12.89 g (0.064 mol) of the tetralone in 120 ml of THF was added to the Grignard reagent prepared from 24 ml of vinyl bromide and 6.3 g of magnesium in 160 ml of THF. Following 16 hr standing at room temperature the reaction mixture was treated with 100 ml of saturared ammonium chloride and the product isolated in the usual way. The resulting oil still showed a sizable CO band (1680 cm^{-1}) in the ir. The oil was again treated with the same quantity of vinyl magnesium bromide as above. The crude carbinol was obtained as a viscous oil.

3-Methoxy-7,7-dimethyl-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (8).—A mixture of 18.39 g (0.079 mol) of the crude vinylcarbinol, 7.05 g (0.063 mol) of 2-methylcyclopentane-1,3-dione, and 0.6 g of potassium hydroxide in 250 ml of methanol was heated at reflux for 4 hr. The bulk of the solvent was removed *in vacuo* and the residue dissolved in ether and 100 ml of 1 *N* sodium hydroxide. The organic layer was washed in turn with two further portions of 100 ml of 1 *N* sodium hydroxide, water, and brine. The solid which was obtained when the solution was taken to dryness was chromatographed over 2 l. of Florisil (elution with 3% acetone in Skellysolve B). There was obtained 15.12 g (59%) of the diketone, mp 79–82.5°.

The analytical sample (obtained from petroleum ether, bp 30–60°) melted at 83–86°. The nmr is in good agreement with the structure. *Anal.* Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.02; H, 8.06.

***dl*-3-Methoxy-7-7-dimethyl-8,14-secoestra-1,3,5(10),8-tetraene-14,17-dione (9).**—A solution of 0.50 g (1.5 mmol) of the diketone 8 and 10 mg of *p*-toluenesulfonic acid in 50 ml of benzene was heated at reflux for 6 hr. The solution was allowed to cool, diluted with ether, and washed with sodium bicarbonate and brine. The solid which remained when the solution was taken to dryness was recrystallized several times from petroleum ether to give crystals: mp 76–79°; mmp (with starting material) 69–80°; nmr broad singlet at δ 5.36, complex A_2B_2 centered at δ 2. *Anal.* Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.47; H, 8.28.

***dl*-3-Methoxy-7,7-dimethyl-14β-estra-1,3,5(10),8,15-pentaen-17-one (10).**—The powdered dione (2.50 g, 7.7 mmol) was quickly added to 50 ml of well-stirred ice-cold 8.5 *N* hydrogen chloride in ethanol. At the end of 10 min the dark solution was poured into saturated sodium bicarbonate. The precipitate was taken up in ether, washed with water and brine, and taken to dryness. The residual slightly gummy solid was recrystallized from Skellysolve B to afford 1.54 g (65%) of the tetracyclic ketone, mp 144–147°. Further recrystallization gave a sample of the steroid: mp 146–148°; nmr complex aromatic region (3 H) doublet of doublets at δ 7.6 and 6.1 (2 H), singlet at 3.8 (3 H), broad band centered at 3.45 (1 H), singlet at 3.2 (2 H), broad multiplet 2.6–1.5 (4 H), singlet at 1.25 (6 H), singlet at 1.10 (3 H). *Anal.* Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.61; H, 8.07.

***dl*-3-Methoxy-7,7-dimethyl-14β-estra-1,3,5(10),8-tetraen-17-one (12).**—A mixture of 1.65 g (5.4 mmol) of the pentaene and 0.20 g of 10% palladium on charcoal in 200 ml of benzene was shaken under an atmosphere of hydrogen until the uptake of gas stopped (35 min). The catalyst was collected on a filter and the solution taken to dryness. The residual solid was recrystallized from aqueous methanol to give 1.40 g (85%) of product, mp 98–105°.

The analytical sample from an earlier run melted at 104–106°. *Anal.* Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.85; H, 8.47.

***dl*-3-Methoxy-7,7-dimethyl-14β-estra-1,3,5(10),8-tetraen-17α-ol (13).**—To a solution of 1.40 g (4.5 mmol) of the ketone in 60 ml of methanol there was added 0.40 g of sodium borohydride. The mixture was stirred at room temperature for 4 hr and the bulk of the solvent removed *in vacuo*. The residue was dissolved in ether and water and the organic layer washed with water and brine. The solid which remained when the solution was taken to dryness was recrystallized from Skellysolve B to afford 1.33 g (95%) of crystals, mp 126.5–128.5°. *Anal.* Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.59; H, 9.21.

***dl*-3-Methoxy-7,7-dimethyl-8α,14β-estra-1,3,5(10)-trien-17α-ol (15). and *dl*-3-Methoxy-7,7-dimethyl-8α,14β-estra-2,5(10)-dien-17α-ol (14).**—Liquid ammonia (60 ml) was distilled from over sodium into a well-stirred solution of 0.50 g (1.6 mmol) of the tetraene in 1 ml of *tert*-butyl alcohol in 30 ml of THF. Approximately one-third of a 50-mg (7.4 mmol) portion of lithium was then added. The remaining metal was added as soon as the color had faded. At the end of 30 min, 1 g of ammonium chloride was added to the mixture. The solvent was evaporated under a stream of nitrogen and the residue dissolved in ether and water. The organic layer was washed with water and brine and taken to dryness. The residual gum was carefully chromatographed on 50 ml of silica gel (elution with 10% acetone in Skellysolve B) to afford first the enol ether as crystals followed by the triene as a series of gums which crystallized on trituration with cyclohexane.

The former (125 mg, 24.8%) was recrystallized from aqueous methanol to mp 117–118°. *Anal.* Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.05; H, 10.11.

The second fraction was recrystallized from cyclohexane to give 0.25 g (49%) of the triene as its cyclohexane solvate (confirmed by nmr), mp 75–85°. *Anal.* Calcd for $C_{21}H_{30}O_2 \cdot C_6H_{12}$: C, 81.35; H, 10.65. Found: C, 81.26; H, 10.73.)

Reduction of 14 to 15.—Proceeding exactly as above a solution of 5.30 g (0.017 mol) of the triene and 10 ml of *tert*-butyl alcohol in 300 ml of THF and 600 ml of liquid ammonia was treated with 0.77 g (0.11 g-atom) of lithium. Following 1.5 hr of stirring the product was worked up as previously. The crude product was chromatographed (silica gel, 5% acetone in Skellysolve B) and then recrystallized to afford 2.67 g (50%) of enol ether, mp 118–120°, identical with that obtained above.

***dl*-7,7-Dimethyl-8α,14β-estr-4-ene-3,17-dione (17) and *dl*-7,7-Dimethyl-8α,14β-estr-5(10)-ene-3,17-dione (16).**—A solution of 2.10 g of the enol ether and 20 ml of 2.5 *N* hydrochloric acid in 60 ml of methanol was allowed to stand at room temperature overnight. The mixture was worked up in the usual way to afford the testosterones as a gum. An ice-cooled, well-stirred solution of the gum in 80 ml of acetone was treated dropwise with 4.2 ml of Jones reagent. The mixture was concentrated on the rotary evaporator and the residue dissolved in ether and water. The organic layer was washed with water and brine and taken to dryness. The residual gum was carefully chromatographed on 200 ml of silica gel (elution with 10% acetone in Skellysolve B) to give first 0.23 g (11%) of crystalline unconjugated ketone followed by 1.13 g (57%) of the conjugated enone. The former was recrystallized from petroleum ether (cooling in freezer) to mp 87.5–89.5°, ν_{max} 1745, 1710 cm^{-1}. *Anal.* Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.95; H, 9.46.

The second fraction was recrystallized from ether–Skellysolve B to give 0.93 g of crystals: mp 145–148°; ν_{max} 1745, 1660, 1610 cm^{-1}; λ_{max} 242 nm (ε 17,340). *Anal.* Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.37; H, 9.47.

17α-Hydroxy-7,7-dimethyl-8α,14β-estr-4-en-3-one *p*-Bromobenzoate (18).—Butyllithium in pentane (1.1 ml of 1.55 *N*) was added to 500 mg (1.6 mmol) of the steroid alcohol in 10 ml

(15) A synthetic magnesia–silica gel absorbent manufactured by the Floridin Co., Warren, Pa.

(16) A petroleum fraction, bp 60–70°, sold by the Skelly Oil Co.

TABLE V

FINAL POSITIONAL AND THERMAL PARAMETERS AND THEIR STANDARD DEVIATIONS (IN PARENTHESES)[a]

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Br(1)	−10320 (16)	−7607 (58)	50000 (0)	264 (9)	3146 (110)	499 (18)	−316 (63)	33 (29)	46 (98)
Br(2)	−19938 (16)	64874 (58)	57163 (34)	311 (10)	3136 (111)	580 (21)	308 (68)	−240 (29)	176 (105)

Atom	x	y	z	B	Atom	x	y	z	B
O(1)	3487 (10)	2063 (36)	2293 (15)	10.84 (0.94)	O(1′)	2367 (11)	3700 (38)	8337 (14)	9.72 (0.89)
O(2)	579 (9)	5289 (30)	4094 (12)	7.04 (0.71)	O(2′)	−536 (9)	139 (28)	6772 (12)	6.50 (0.68)
O(3)	−53 (9)	6930 (36)	4252 (14)	8.82 (0.78)	O(3′)	−1249 (8)	−1328 (33)	6758 (13)	7.31 (0.72)
C(1)	2192 (15)	2349 (55)	2518 (22)	8.59 (1.26)	C(1′)	1074 (12)	3340 (43)	8191 (17)	4.88 (0.91)
C(2)	2629 (16)	2683 (52)	2153 (22)	8.77 (1.29)	C(2′)	1535 (13)	3093 (41)	8562 (18)	5.32 (0.98)
C(3)	3131 (19)	2510 (59)	2563 (26)	10.90 (1.45)	C(3′)	1962 (18)	3377 (60)	8172 (26)	9.70 (1.30)
C(4)	3113 (14)	3055 (49)	3227 (22)	7.22 (1.14)	C(4′)	1986 (15)	2780 (48)	7536 (21)	6.95 (1.14)
C(5)	2682 (14)	3675 (47)	3452 (20)	5.94 (1.02)	C(5′)	1560 (15)	2162 (47)	7308 (20)	6.99 (1.16)
C(6)	2715 (11)	4493 (43)	4060 (19)	4.47 (0.89)	C(6′)	1488 (13)	1327 (45)	6586 (19)	6.61 (1.06)
C(7)	2321 (12)	3829 (42)	4488 (19)	4.47 (0.92)	C(7′)	1035 (13)	1821 (43)	6255 (19)	6.04 (0.99)
C(8)	1806 (11)	4063 (43)	4133 (18)	5.35 (0.95)	C(8′)	593 (10)	1385 (40)	6628 (15)	3.53 (0.82)
C(9)	1823 (11)	2979 (40)	3564 (17)	4.40 (0.96)	C(9′)	627 (10)	2541 (35)	7214 (16)	2.92 (0.78)
C(10)	2183 (12)	3656 (47)	3052 (18)	5.38 (0.98)	C(10′)	1045 (14)	2088 (44)	7640 (18)	5.76 (0.99)
C(11)	1325 (12)	3112 (45)	3289 (18)	5.63 (1.03)	C(11′)	144 (12)	2429 (44)	7548 (16)	5.38 (1.02)
C(12)	1222 (11)	4946 (44)	3033 (17)	5.09 (1.03)	C(12′)	74 (11)	430 (40)	7853 (17)	3.97 (0.84)
C(13)	1309 (12)	6382 (47)	3569 (18)	5.15 (0.96)	C(13′)	156 (12)	−903 (47)	7283 (20)	6.69 (1.04)
C(14)	1674 (11)	6056 (45)	4014 (18)	5.83 (1.01)	C(14′)	537 (11)	−491 (42)	6735 (18)	4.81 (0.93)
C(15)	1469 (12)	6989 (39)	4618 (16)	4.63 (0.95)	C(15′)	292 (13)	−1363 (51)	6201 (20)	7.93 (1.15)
C(16)	1034 (13)	7918 (42)	4466 (17)	5.85 (0.98)	C(16′)	−169 (13)	−2463 (44)	6419 (19)	6.38 (1.09)
C(17)	839 (12)	7059 (50)	3933 (18)	7.57 (1.22)	C(17′)	−301 (13)	−1545 (50)	6959 (21)	7.79 (1.13)
C(18)	1440 (12)	8188 (43)	3189 (17)	5.63 (1.00)	C(18′)	305 (14)	−2565 (50)	7657 (20)	7.61 (1.17)
C(19)	2344 (11)	4859 (39)	5054 (21)	5.74 (0.97)	C(19′)	1075 (12)	802 (42)	5651 (18)	6.63 (0.99)
C(20)	2390 (13)	1869 (48)	4639 (18)	7.03 (1.17)	C(20′)	1040 (16)	3957 (60)	6063 (22)	12.75 (1.54)
C(21)	109 (15)	5621 (57)	4243 (21)	7.50 (1.12)	C(21′)	−1037 (15)	−59 (51)	6681 (19)	6.50 (1.07)
C(22)	−120 (13)	3899 (47)	4416 (17)	4.76 (0.92)	C(22′)	−1242 (13)	1746 (52)	6466 (18)	5.49 (1.00)
C(23)	−624 (15)	4200 (51)	4590 (19)	7.69 (1.18)	C(23′)	−1770 (12)	1437 (51)	6407 (18)	6.17 (1.02)
C(24)	−887 (13)	2642 (55)	4779 (18)	7.45 (1.21)	C(24′)	−1950 (13)	3095 (50)	6234 (18)	6.41 (1.07)
C(25)	−672 (13)	1046 (46)	4716 (16)	5.21 (1.01)	C(25′)	−1657 (15)	4639 (52)	6063 (20)	7.66 (1.20)
C(26)	−171 (13)	904 (46)	4609 (17)	5.79 (1.03)	C(26′)	−1189 (12)	4681 (46)	6165 (17)	4.60 (0.97)
C(27)	95 (12)	2310 (51)	4452 (18)	5.80 (1.05)	C(27′)	−976 (12)	3238 (51)	6341 (18)	5.45 (0.94)

[a] Coordinates and anisotropic temperature factors of Br atoms are multiplied by 10^5. Coordinates of C and O atoms are multiplied by 10^4. The z coordinate of Br(1) was held fixed because of the polar space group.

of benzene, followed by 370 mg of *p*-bromobenzoyl chloride. After 48 hr the mixture was poured into ether and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and taken to dryness. The residue was chromatographed on two 25-g silica gel plates (development with methylene chloride). The less polar zone was scraped off and eluted to give 0.43 g of crude acylated enol ether. A solution of that gum and 3.3 ml of 2.5 *N* hydrochloric acid in 10 ml of THF was allowed to stand for 2 days. The solvent was removed *in vacuo* and the residue taken up in ether. This last solution was washed with water and brine and taken to dryness. The residue was chromatogaphed on two preparative silica gel plates (20% acetone in Skellysolve B). The major zone was collected as above. The resulting solid was recrystallized twice from ether–Skellysolve B to yield 200 mg (26%) of product, mp 118.5–120°. *Anal.* Calcd for $C_{27}H_{33}BrO_3$: C, 66.80; H, 6.85; mol wt, 484. Found: C, 66.68; H, 7.17; mol wt, 484, 486.

X-Ray Analyis of 18. A. Crystal data: orthorhombic; space group $Pna2_1$; $a = 28.28 \pm 0.04$, $b = 7.84 \pm 0.02$, $c = 22.00 \pm 0.03$ Å, $Z = 8$, $V = 4880 \pm 14$ Å^3, $\rho_{calcd} = 1.319$ g/cc. The crystals are small, clear plates. Weissenberg and precession photographs showed that the crystals are orthorhombic, with systematic absences in the $0kl$ plane for $k + l = 2n + 1$, and in the $h0l$ plane for h odd. Possible space groups were therefore limited to $Pna2_1$, which is acentric, with a multiplicity of 4, and (with axes permuted), $Pnma$, which is centric and has a multiplicity of 8. Unit cell volume and molecular weight indicated 8 molecules in the unit cell.

Three-dimensional intensity data were gathered on the UPACS computerized diffractometer system (a General Electric diffractometer with an Electronics and Alloys full-circle orienter, Datex automated, controlled by an IBM 1800 computer). The crystal orientation was determined by the computer before the data collection. Nickel-filtered Cu K radiation was used. The θ–2θ scan technique was employed with 3.6° scans at 2°/min and with 30-sec background observations at each end of the scan. Four reflections were monitored periodically during the data collection. By the end of the data collection, check reflections had lost 25% of their original intensity. A correction for decay was made by using check intensities to fit a deterioration scale scale factor as a polynomial function of time.

For weighting purposes, $\sigma(I)$ for each reflection was approximated by

$$\sigma(I) = [\sigma^2(I)_{\substack{\text{counting}\\\text{statistics}}} + (dI)^2]^{1/2}$$

where d (= 0.0288) was estimated by the data reduction program from check reflection variation (after deterioration correction). The usual adjustments were made on the data: Lorentz and polarization corrections; absorption correction[17] (transmissions ranged from 68 to 91%); and Wilson scaling to place the data on an approximate absolute scale. Standard propagation of error methods were used to carry standard deviations through all these calculations.

Crystal quality was not good enough to obtain data at high 2θ values. Intensities of almost all reflections with a 2θ angle greater than 90° were less than three times their standard deviations; accordingly, 90° was used as a cut-off point for the data. The data were edited by deletion of all reflections with intensities less than twice their standard deviations. The final data set contained only 1176 reflections.

B. Trial Solution.—A trial solution for the bromine position was found by Patterson analysis, postulating space group $Pna2_1$ with 2 symmetry-independent molecules in the unit cell. Most of one molecule was obvious in the first electron density map when reflections were phased according to contributions from the two bromines only. Two more structure-factor and electron-density calculations were needed to get starting coordinates for all the atoms.

C. Refinement.—Coordinates were refined using multiple-matrix least squares; the function minimized was $\Sigma w[|F_o|^2 - |F_c|^2]^2$.

The weighting function used at first was the Hughes $1/F_o$ type.

(17) W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **10**, 180 (1957).

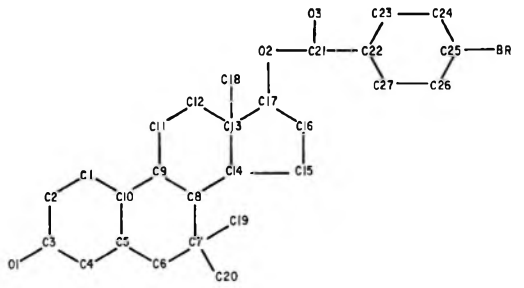


Figure 2.—Numbering.

After several cycles of refinement, w was set equal to the reciprocal of $\sigma^2(F_0^2)$ which was estimated during data reduction.

Because of the size (62 symmetry-independent atoms), the 259 refinable parameters were split into several matrices. All temperature factors were in one matrix together with the scale factor for F_0. Since a strong pseudosymmetric relation between the two molecules was noted, the coordinate matrix scheme was designed to put like parts of the molecules together in three different matrices. Anisotropic temperature factors for the bromine atoms were refined, but the data were judged not suitable for determination of anisotropic temperature factors on carbon and oxygen atoms or for determination of hydrogen atom coordinates. The addition of these parameters would have brought the total number of refinable parameters to 638, too many to determine with only 1176 observations. Refinement was terminated when all shifts were less than $^1/_4$ of corresponding standard deviations.

The final value of the R index ($R = \Sigma||F_0| - |F_c||/\Sigma|F_0|$) was 0.111; the standard deviation of fit, $[(\Sigma w[|F_0|^2 - |F_c|^2]^2)]^{1/2}/(m - s)^{1/2}$, was 2.29

Final parameters are given in Table V for both symmetry independent molecules.[18] The numbering scheme is shown in Figure 2. Numbering follows the convention for steroids as far as possible; C(1) through C(18) have conventional numbering.

The remainder of the atoms are numbered C(19)–C(27) and O(1)–O(3). Bond distances and angles are given in Tables II and III.

All calculations were carried out on IBM 360/30 and IBM 360/50 computers using the programs of the CRYM crystallographic system developed by one of the authors (D. J. D.). Atomic form factors are from "International Tables for X-Ray Crystallography."[19]

Registry No.—**3**, 25380-93-2; **4**, 25380-94-3; **5**, 25380-95-4; **6**, 25380-96-5; **7**, 25380-97-6; **8**, 25380-98-7; **9**, 31020-45-8; **10**, 31025-03-3; **12**, 31025-04-4; **13**, 31025-05-5; **14**, 31025-06-6; **15**, 31025-07-7; **16**, 31025-08-8; **17**, 31025-09-9; **18**, 31025-10-2.

(18) Listings of observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(19) "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, (1962), pp 202–205.

Synthesis of Racemic Muscone and Cyclopentadecanone (Exaltone) from 1,9-Cyclohexadecadiene

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Muscone (11) and exaltone (19) have been synthesized from 1,9-cyclohexadecadiene (1). Unsaturated monoepoxide 2 upon treatment with butyllithium was converted into an α,β-unsaturated alcohol 3 and oxidized with chromic acid into the corresponding ketone 5. This, upon treatment with methylmagnesium bromide in the presence of cuprous chloride, was converted into β-methylcyclohexadecenone (6) and then hydrogenated to β-methylcyclohexadecanone (7). The dibromide of 7 underwent a Favorski rearrangement to produce a mixture of 3-methyl and 15-methyl cyclopentadecene-1-carboxylate (7:3) which on treatment with hydrazoic acid was converted into muscone (11) and 2-methylcyclopentadecanone (12), respectively. In a similar way, 1-carboxymethyl-1-cyclopentadecene (18) obtained from dibromocyclohexadecanone was converted into exaltone (19). In another experiment, saturated epoxide 13 was rearranged to the allylic alcohol 15 and oxidized to the unsaturated ketone 16 which was then converted to 7.

Muscone (11) [(−)-3-methylcyclopentadecanone] is the principal odorous constituent of musk pod obtained from the male deer *Moschus Moschiferus*. Owing to its rare occurrence in nature and its exotic and useful odor, many routes[1] have been developed for the synthesis of muscone. This paper reports a synthesis of (±)-muscone (11) and exaltone (19) from 1,9-cyclohexadecadiene (1).[2]

Addition of 1 mol of peracetic acid to diene 1 (three isomers, cis,cis, trans,trans, and cis,trans) yielded 69% of unsaturated monoepoxide 2 (four isomers, cis,cis, trans,trans, cis,trans, and trans,cis). All these isomers were separable on an analytical glc column. It should be noted that these unsaturated monoepoxides 2 and the corresponding saturated epoxides 13 possess weak musk odor.

Treatment of 2 with 1 mol of butyllithium[3,4] afforded a mixture of α,β-unsaturated secondary alcohol 3 (50%) and cyclohexadecenone 4. Attempts to convert 2 to 3 with other reagents, *viz.*, alumina[5] and aluminum isopropoxide,[6] were not successful. The allylic alcohol 3 thus formed was isolated by column chromatography and then oxidized to the corre-

(1) (a) K. Ziegler and K. Weber, *Justus Liebigs Ann. Chem.*, **521**, 164 (1934); (b) L. Ruzicka and M. Stoll, *Helv. Chim. Acta*, **17**, 1308 (1934); (c) H. Hunsdiecker, *Ber. Deut. Chem. Ges. B*, **75**, 1190, 1197 (1942); (d) M. Stoll and K. Commarmont, *Helv. Chim. Acta*, **31**, 554 (1948); (e) A. T. Blomquist and R. D. Spenser, *J. Amer. Chem. Soc.*, **69**, 472 (1947); **70**, (1948); (f) A. T. Blomquist, R. W. Holley, and R. D. Spenser, *ibid.*, **70**, 34 (1948); (g) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **30**, 2019 (1947); (h) M. S. R. Nair, H. H. Mathur, and S. C. Bhattacharyya, *J. Chem. Soc.*, 4154 (1964); (i) V. R. Mamdapur, P. P. Pai, K. K. Chakravarti, U. G. Nayak, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 2601 (1964); (j) G. Ohloff, J. Becker, and K. H. Schulte-Elte, *Helv. Chim. Acta*, **50**, 705 (1967); (k) A. Eschenmoser, D. Felix, and G. Ohloff *ibid.*, **50**, 708 (1967); (l) H. Nozaki, H. Yamamoto, and T. Mori, *Can. J. Chem.*, **47**, 1107 (1969); (m) E. Yoshii and S. Kimoto, *Chem. Pharm. Bull.*, **17**, 629 (1969).

(2) N. Calderon, E. A. Ofstead, and W. A. Judy, *J. Polym. Sci.*, **5**, 2209 (1967).

(3) H. Nozaki, T. Mori, and Noyori, *Tetrahedron*, **22**, 1207 (1966).

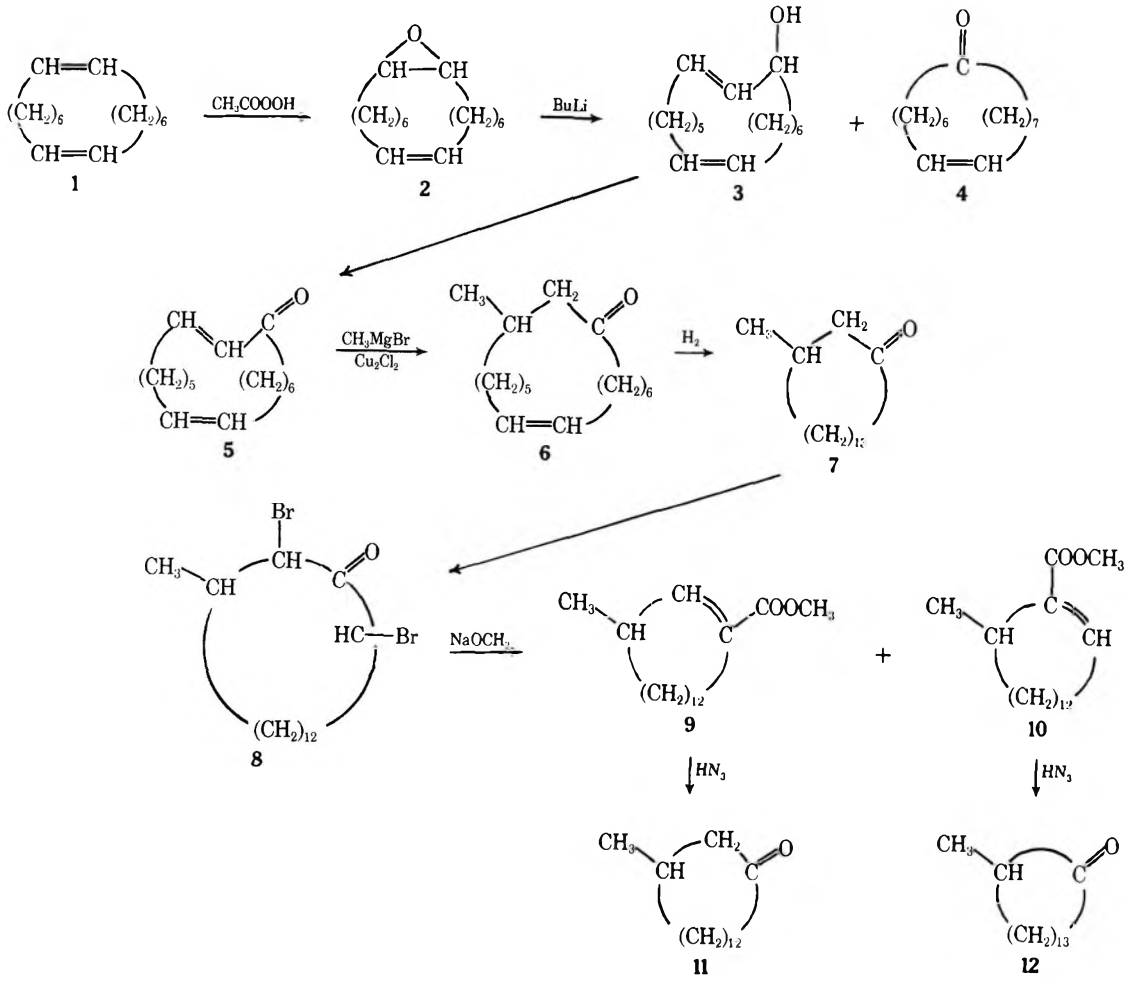
(4) K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, **51**, 494 (1968).

(5) V. S. Joshi, N. P. Damodaran, and Sukh Dev, *Tetrahedron*, **24**, 5817 (1968).

(6) E. H. Eschinasi, *Israel J. Chem.*, **6**, 713 (1968).

SCHEME I

REARRANGEMENT OF UNSATURATED MONOEPOXIDE 2



sponding α,β-unsaturated ketone **5**[7] (69%). A 1,4 addition of methyl Grignard to **5** in the presence of cuprous chloride and ether[1d] went smoothly to produce 15-methyl-8-cyclohexadecen-1-one (**6**, 83%), which was purified by column chromatography and hydrogenated to 3-methylcyclohexadecanone (**7**).

Recently Garbisch[8] showed that cyclododecanone could be converted to cycloundecanone in good yield. We applied this method to cyclohexadecanone **17**. Bromination of **17** yielded dibromocyclohexadecanone, which on treatment with sodium methoxide underwent Favorskii rearrangement to the unsaturated ester **18**, which was converted to exaltone **19** in 78% yield by the Curtius reaction.

The same method was applied to **7**, bromination of which gave a quantitative yield of dibromo ketone **8**. When this dibromo ketone was treated with sodium methoxide for a short period of time, **9** and **10** were formed in the ratio of 7:3. These two esters were separated by careful column chromatography. On treatment with a mixture of sodium azide and sulfuric acid and then with steam, unsaturated esters **9** and **10** were smoothly converted to racemic muscone (**11**) and 2-methylcyclopentadecanone (**12**), respectively (Scheme I).

As an alternative method, the saturated epoxide **13** was also rearranged to allylic (trans)[9] alcohol **15**[10] (62%) and 1,3-cyclohexadecadiene (**14**, 4%) by means of lithium diethylamide.[11] Alcohol **15** was oxidized to the corresponding ketone **16** (70%) which was then converted to **7** (80%) by the methylmagnesium bromide–cuprous chloride method (Scheme II).

Experimental Section

Melting points were uncorrected. Glc analyses were performed on F & M 810 instrument using 5% Carbowax 20M and 5% silicone SE-30 coated on Anakrom ABS (80–100 mesh) packed in a stainless steel column (0.25 in. × 25 ft). The following spectrometers were used: ir, Beckman IR-5A and IR-4; nmr, Varian HA-100 (CCl_4, TMS as internal standard); mass spectra, CEC Model 21-110 and AEI-MS9 for high-resolution spectra. Mass spectral major fragmentation peaks were recorded in decreasing order of intensity. Deactivated silicic acid (5%) made by adding 5 ml of water to 95 g of silicic acid (Grace, 100–200 mesh) and alumina, neutral, (Fisher Scientific, 80–200 mesh) were used for column chromatography.

17-Oxobicyclo[14.1.0]heptadec-8-ene (2).—A solution of 40% peracetic acid (37.6 g, 0.18 mol) in methylene chloride (50 ml) was added dropwise to a stirred solution of 1,9-cyclohexadecadiene (**1**, 40 g, 0.18 mol) and sodium acetate (56 g) in methylene chloride (250 ml) at 0–5°. When the addition was completed,

(7) In another experiment ketone **5** was made in 9% yield by the autoxidation of **1**. Our attempts to make the α,β-unsaturated ketone **5** by either selenium dioxide or chromium trioxide oxidation of **1** were not very successful.

(8) E. W. Garbisch, Jr., and J. Wohllebe, *J. Org. Chem.*, **33**, 2157 (1968).

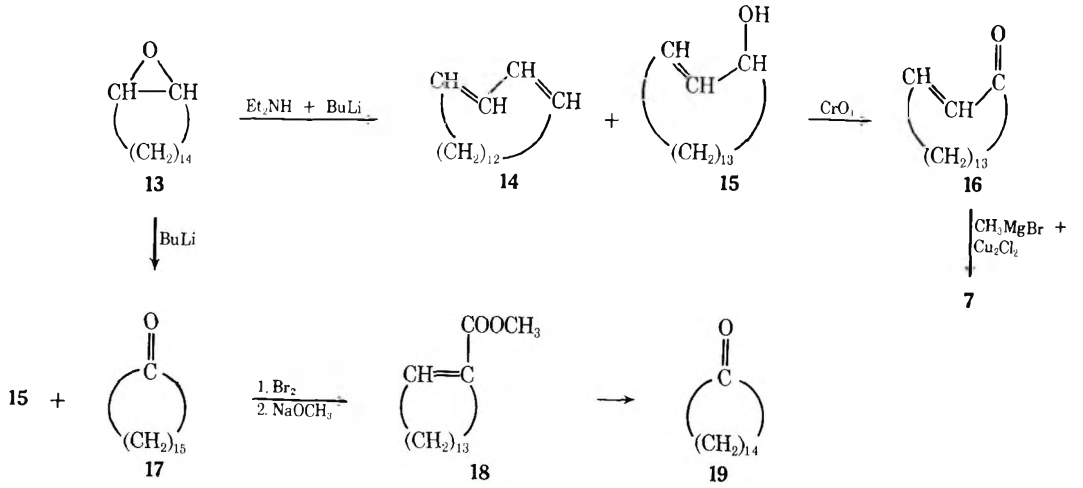
(9) During the rearrangement of epoxides **2** and **13** to allylic secondary alcohols **3** and **15** by alkyllithium, the new double bond thus formed on the ring was trans.

(10) When saturated epoxide **13** was treated with butyllithium, the yield of **15** and **17** was 19 and 54%, respectively.

(11) J. K. Crandall and L.-H. C. Lin, *J. Org. Chem.*, **33**, 2375 (1968).

SCHEME II

REARRANGEMENT OF SATURATED EPOXIDE 13



the solution was stirred for an additional 3 hr at 0–5° and then allowed to reach room temperature. Water (200 ml) was added and the two phases separated. The aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with saturated sodium chloride solution and dried (Na_2SO_4). Removal of the solvent yielded 42 g of crude material which was chromatographed on deactivated silicic acid (500 g)–20% ether in hexane (2 l.) eluted 30 g (yield 69%) of epoxide **2**. Glc analysis showed four peaks. The mass spectrum of the mixture of these four isomers **2** showed a molecular ion peak at *m/e* 236 and other major peaks at *m/e* 55, 67, 41, 81, 95; ir (neat) (mixture of four isomers) 3.41, 3.5, 6.9, 7.25, 7.3, 9.9, 10.35, 13.5, 14.0 μ; nmr (mixture of four isomers) δ 1.35 (m with a s at 1.35, internal methylene), 2.0 (b, 4 H, $CH_2C{=}CCH_2$), 2.5 (m, 1 H, epoxy CH), 2.7 (m, 1 H, epoxy CH), 5.3 (m, 2 H, CH=CH).

Anal. Calcd for $C_{16}H_{28}O$: *m/e* 236.2140. Found: *m/e* 236.2137.

Reaction of Monoepoxide 2 with Butyllithium.—A solution of **2** (23.6 g, 0.1 mol) in hexane (100 ml) was added dropwise over a 1.5-hr period to a stirred solution of 15% butyllithium (80 ml, 0.13 mol) in hexane at 0° under nitrogen. After the addition was complete, the mixture was stirred for an additional 0.5 hr at 0°. The temperature was then slowly raised to 65°, and the mixture refluxed for 3 hr. The reaction mixture was cooled to 5° and water (30 ml) was added. The organic layer was separated, washed with water, dried (Na_2SO_4), and on removal of solvent yielded 24 g of crude product which was chromatographed on silicic acid (300 g)–10% ether in hexane eluted an 11.1-g mixture of unreacted epoxide **2** (minor amount) and cyclohexadecenone **4**[12] (major product); 20–40% ether in hexane eluted 12 g (yield 50.8%) of alcohol **3**. Glc of **3** showed two peaks. The mass spectrum of 2-*trans*-9-*trans*-cyclohexadecadien-1-ol (**3**) showed a peak at *m/e* 218 (M − 18) and other major peaks at *m/e* 41, 67, 79, 39, 80, 81; ir (neat) 3.0 (strong, OH), 3.5, 6.05 6.99, 7.45, 7.7, 9.8 (C=CCHOH), 10.35 (strong, trans CH=CH), 14.0 μ (broad, medium). The mass spectrum of 2-*trans*-9-*cis*-cyclohexadecadien-1-ol (**3**) showed a peak at *m/e* 218 (M − 18) and other major peaks at *m/e* 41, 67, 79, 80, 39, 81; ir (neat) 3.0 (strong, OH), 3.5, 6.1, 7.0, 7.5, 7.8, 9.45, 9.85 (C=CCHOH), 10.4 (medium, *trans* CH=CH), 14.1 μ (broad, strong); nmr (mixture of *cis*- and *trans*-**3**) δ 1.33 (m with a s at 1.33, internal methylene), 2.0 (b, 6 H, $CH_2C{=}C$), 3.94 (b, 1 H, CHO), 5.3 (m, 4 H, CH=CH).

Anal. Calcd for $C_{16}H_{28}O$: *m/e* 236.2140. Found: *m/e* 236.2151.

Chromium Trioxide Oxidation of 3.—A solution of chromium trioxide (10 g) in concentrated sulfuric acid (11 ml) and water (50 ml) was cautiously added to a stirred solution of **3** (12 g) in acetone (300 ml) at 0° until an orange-yellow color persisted. The solution was stirred for an additional 3 hr at 0° and allowed to reach room temperature. Half of the acetone (150 ml) was removed under reduced pressure without heat. Water (200 ml) was added and then extracted with methylene chloride. The methylene chloride extract was washed with saturated sodium chloride, dried (Na_2SO_4), and on removal of solvent produced an oil (10 g) which was chromatographed on silicic acid (120 g)–5–15% ether in hexane eluted 8.3 g (yield 69.1%) of ketone **5** whose glc (Carbowax 20M) showed two peaks. The mass spectrum of 2-*trans*-9-*trans*-cyclohexadecadien-1-one (**5**) showed molecular ion peak at *m/e* 234 and other major peaks at *m/e* 41, 67, 55, 81; ir (neat) 3.35 (very weak), 3.45, 3.55, 5.88, and 5.95 (sh) of 6.02 (C=CC=O), 6.19, 6.99, 7.35, 7.45, 7.8, 8.0, 8.12, 8.3, 10.35 (strong, trans CH=CH), 13.9 μ (broad, weak). The mass spectrum of 2-*trans*-9-*cis*-cyclohexadecadien-1-one (**5**) showed molecular ion peak at *m/e* 234 and other major peaks at *m/e* 41, 67, 55, 81; ir (neat) 3.35 (weak), 3.45, 3.54, 5.89 (weak, sh), 5.95 and 6.04 (almost equal intensity, C=CC=O), 6.2, 6.9, 7.49, 7.8, 8.0, 8.3, 9.0 (broad, weak), 9.79, 10.25 (medium, trans CH=CH), 14.0 μ (broad, cis CH=CH); nmr (mixture of *cis*- and *trans*-**5**) δ 2.0 (b, 4 H, $CH_2C{=}CCH_2$), 2.39 (m, 4 H, $CH_2C{=}CCOCH_2$), 5.24 (m, 2 H, CH=CH), 5.88–6.14 and 6.50–6.85 (m, 2 H, CH=CHC=O).

Anal. Calcd for $C_{16}H_{26}O$: *m/e* 234.1983. Found: *m/e* 234.1976.

15-Methyl-8-cyclohexadecen-1-one (6).—A solution of **5** (5.5 g, 0.023 mol) in anhydrous ether (40 ml) was added slowly over 1.5 hr to a stirred mixture of cuprous chloride (0.15 g) and methylmagnesium bromide (10 ml, 0.03 mol) in anhydrous ether (40 ml) at 10°. Stirring was continued for an additional 1 hr at 10°. Cold 10% hydrochloric acid (25 ml) was added. The ether layer was separated, washed first with a 10% sodium bicarbonate solution and then with water, and dried (Na_2SO_4). Evaporation of solvent yielded 5.7 g of an oil which was chromatographed on silicic acid (50 g)–5–20% ether in hexane eluted 4.9 g (yield 83.4%) of **6** whose glc (Carbowax 20M) showed two peaks. The mass spectrum of 15-methyl-8-*trans*-cyclohexadecen-1-one (**6**) showed molecular ion peak at *m/e* 250 and other major peaks 41, 55, 67, 69, 27, 81; ir (neat) 3.45, 3.55, 5.89 (C=O), 6.9, 6.95, 7.13, 7.35, 7.8, 9.0, 9.7, 10.35 (strong, trans CH=CH), 14.0 μ (weak). The mass spectrum of 15-methyl-8-*cis*-cyclohexadecen-1-one (**6**) showed molecular ion peak at *m/e* 250 and other major peaks at *m/e* 41, 55, 67, 69, 81, 27; ir (neat) 3.35 (weak and broad), 3.45, 3.52, 5.89 (C=O), 6.9, 6.95 (sh), 7.12, 7.35, 7.85, 9.0, 9.7, 14.0 μ (strong, broad); nmr (mixture of *cis*- and *trans*-**6**) 0.9 (q, 3 H, CH_3CH), 1.98–2.30 (m, 7 H, $CHCH_2COCH_2CH_2$), 5.3 (m, 2 H, CH=CH).

Anal. Calcd for $C_{17}H_{30}O$: *m/e* 250.2296. Found: *m/e* 250.2271.

3-Methylcyclohexadecanone (7).—A solution of **6** (10 g) in methanol (200 ml) was hydrogenated under normal temperature and pressure using 10% palladium on carbon (1.5 g) as a catalyst. After usual work-up 10 g of 3-methylcyclohexadecanone (**7**) was obtained. Glc of **7** gave one peak whose mass spectrum showed a molecular ion peak at *m/e* 252 and other major peaks at 41, 55, 43, 42, 69, 85; ir (neat) 3.41, 3.5, 5.83 (C=O), 6.85, 7.09, 7.3, 7.8, 8.7, 8.9, 9.15, 9.6, 14.0 μ (broad); nmr δ 0.92 (d, J = 6 Hz, 3 H, CH_3CH), 1.1–2.0 (m, 25 H, with s at 1.31), 2.0–2.4 (m, 4 H, CH_2COCH_2).

(12) L. G. Wideman, *J. Org. Chem.*, **33**, 4541 (1968).

Anal. Calcd for $C_{17}H_{32}O$: *m/e* 252.2453. Found: *m/e* 252.2450.

3-Methyl-2,16-dibromocyclohexadecanone (8).—Bromine (19.2 g, 0.12 mol) was added dropwise to a solution of **7** (15 g, 0.059 mol) in a mixture of anhydrous benzene (200 ml) and anhydrous ether (20 ml) at 25° over a period of 0.5 hr. The hydrogen bromide thus liberated was removed by connecting the reaction flask to the house vacuum (20 mm) and simultaneously heating the flask to 50°. This operation was continued until the solution of the flask was neutral to litmus paper. This solution was then ready for next step. The mass spectrum of **8** showed molecular ion peaks at *m/e* 408 (M^+) and 410 (M + 2) and other major peaks at *m/e* 112, 55, 41, 69, 98, 249; ir (neat) 3.45, 3.51, 5.81 (C=O), 6.9, 7.29, 7.45, 7.9, 9.0, 9.7 μ; nmr δ 1.07 (d, J = 6.5 Hz, 3 H, CH_3CH), 4.3 (d, J = 6.5 Hz, 1 H, CHBr), 4.5 (t, 1 H, CHBr).

Anal. Calcd for $C_{17}H_{30}OBr_2$: *m/e* 408.0664. Found: *m/e* 408.0657.

3-Methyl 1-Cyclopentadecene-1-carboxylate (9) and 15-Methyl 1-Cyclopentadecene-1-carboxylate (10).—To the reaction flask containing the dibromide **8** from the previous experiment, sodium methoxide (7.6 g, 0.14 mol) was added over a period of 1 hr. Since the reaction was exothermic, the temperature was maintained at 25–30° by an ice bath. The mixture was stirred for an additional 0.5 hr at room temperature and then cooled to 5°. Cold water (200 ml) was added, the organic layer was separated, washed with 5% hydrochloric acid and 50% sodium chloride solution, and dried (Na_2SO_4), and on removal of solvent produced 19 g of crude oil product. Glc (Carbowax 20M) showed two peaks due to **9** (70%) and **10** (30%) which were isolated.

The mass spectrum of **9** showed molecular ion peak at *m/e* 280 and other major peaks at *m/e* 55, 41, 67, 95; ir (neat) 3.45, 3.52, 5.85 (C=CCOOCH$_3$), 6.12, 6.9, and 6.99 (equal intensity), 7.3, 7.45, 7.55, 7.8, 7.9, 8.15 (sh), 8.25, 8.3, 8.6, 8.9, 9.1, 9.35, 9.55, 9.65, 10.0, 11.2 (broad, weak), 14.0 μ (broad, weak); nmr δ 0.93 (d, J = 7 Hz, 3 H, CH_3CH), 3.68 (s, 3 H, $COOCH_3$), 5.46 (d, 1 H, C=CH).

Anal. Calcd for $C_{18}H_{32}O_2$: *m/e* 280.2402. Found: 280.2411.

The mass spectrum of **10** showed a molecular ion peak at *m/e* 280 and other major peaks at *m/e* 41, 55, 81, 67, 95; ir (neat) 3.45, 3.52, 5.85 (C=CCOOCH$_3$), 6.12, 6.9, and 7.0 (equal intensity), 7.25, 7.45, 7.6, 8.1 (sh), 8.25, 8.4, 8.65, 9.0, 9.55, 12.35, 12.75, 13.15, 14.0 μ; nmr δ 1.04 (d, J = 6 Hz, 3 H, CH_3CH), 2.34 (m, 3 H, CH_2C=CCH), 3.7 (s, 3 H, $COOCH_3$), 5.6 (t, 1 H, CH=C).

Anal. Calcd for $C_{18}H_{32}O_2$: *m/e* 280.2402. Found: *m/e* 280.2408.

Mixture of Muscone (11) and 2-Methylcyclopentadecanone (12).—Without further purification the above obtained crude oil (19 g) containing **9** and **10** (7:3) was added to slowly stirred concentrated sulfuric acid (42 ml) at 0°. After stirring for several minutes, chloroform (50 ml) was added and the temperature of the mixture was raised to 40°. Sodium azide (6.2 g, 0.095 mol) was added to the reaction mixture in small portions over a period of 30 min while maintaining the temperature between 35 and 40°. Stirring was continued for 5 min at 40° followed by cooling the reaction mixture to below 5° and then pouring it into wet ice (200 g). Then the whole mixture was steam distilled at a temperature of 100–200° (steam temperature) to obtain approximately 4 l. of distillate. The distillate was saturated with solid sodium chloride and extracted with ether. The ether extract was washed with saturated sodium chloride solution, dried (Na_2SO_4), and on evaporation of solvent yielded 12 g of crude ketone which was chromatographed on silicic acid (200 g)–0–10% ether in hexane yielded 11.1 g (yield 78.7% on the basis of **7**) of liquid containing the mixture of muscone (**11**) and 2-methylcyclopentadecanone (**12**). All our attempts to separate muscone (**11**) from 2-methylcyclopentadecanone (**12**) either by column chromatography or by glc were unsuccessful. The mass spectrum of the mixture of **11** and **12** showed a molecular ion peak at *m/e* 238; ir (neat) 5.85 μ (C=O); nmr (mixture of **11** and **12**) δ 0.9 (d, J = 6 Hz, CH_3CHCH_2C=O), 0.98 (d, J = 6 Hz, CH_3CHC=O), 1.3 (s, internal methylene H), 2–2.5 (m).

Anal. (mixture of **11** and **12**). Calcd for $C_{16}H_{30}O$: *m/e* 238.2296. Found: *m/e* 238.2293.

Separation of 9 and 10 by Column Chromatography.—A mixture of **9** (70%) and **10** (30%) (8.7 g) was first chromatographed on silicic acid (185 g). Ether (3%) in hexane eluted a fraction (fraction **1**, 4.5 g) enriched with **9** (80%); 5–50% ether in hexane eluted another fraction (fraction 2, 3.1 g) which contained **9** and **10** (1:1). By repeated chromatography (five times) of fraction 1 and 2 separately on neutral alumina (activity II, 150–350 g), pure **9** (1.8 g) and a fraction (0.3 g) containing 93% **10** and 7% **9** were obtained.

Muscone (11).—Pure **9** (2 g, 0.007 mol), obtained by the repeated column chromatography, was slowly added to concentrated sulfuric acid (5.2 g) at 5° over 15 min. After this addition chloroform (20 ml) was added to the reaction mixture and warmed to 40°. At this temperature sodium azide (0.6 g, 0.0095 mol) was added in small portions. The mixture was stirred for 15 min at 40°, cooled to 5°, and poured into wet ice (50 g). The whole mixture was then transferred into a microsteam distillation apparatus and steam distilled (pot temperature 160° and head temperature 140°) to obtain approximately 500 ml of distillate. The distillate was saturated with solid sodium chloride and extracted with ether. The ether extract was dried (Na_2SO_4) and on removal of solvent yielded 1.2 g of crude oil which was chromatographed on silicic acid (80 g)–2% ether in hexane (500 ml) eluted 1 g (yield 58.8%) of pure muscone (**11**). Glc (both Carbowax 20M and silicone SE-30) of **11** gave one peak whose mass spectrum showed molecular ion peak at *m/e* 238 and other major peaks at *m/e* 55, 41, 43, 85, 69, 71; ir (neat) 3.42, 3.5, 5.85 (C=O), 6.85, 7.1, 7.3, 7.85, 8.4, 8.7, 8.9, 9.5, 14.0 μ (broad); nmr δ 0.92 (d, J = 6 Hz, 3 H, CH_3CH), 1.1–2.0 (m, 23 H, with s at 1.30), 2.1–2.4 (m, 4 H, CH_2COCH_2). (All these spectral data were superimposable with those of natural muscone.)

Anal. Calcd for $C_{16}H_{30}O$: *m/e* 238.2296. Found: *m/e* 238.2298.

2-Methylcyclopentadecanone (12).—Cyclopentadecene carboxylate **10** (0.15 g containing 7% **9**, obtained by column chromatography) was added to concentrated sulfuric acid (1 ml) at 5°. The mixture turned dark. Chloroform (3 ml) was added and warmed to 40°. Sodium azide (0.1 g) was added over 15 min and stirred for an additional 15 min at 40°. Then the reaction mixture was cooled to 5°, poured into wet ice (15 g), and steam distilled (pot temperature 210° and head temperature 160°) to obtain 300 ml of distillate which was saturated with solid sodium chloride and extracted with ether. The ether extract was dried (Na_2SO_4) and on removal of solvent yielded 0.1 g (yield 78.7%) of 2-methylcyclopentadecanone (**12**). Glc of **12** gave one peak whose mass spectrum showed molecular ion peak at *m/e* 238 and other major peaks at *m/e* 55, 41, 72, 43, 69; ir (neat) 3.45, 3.51, 5.85 (C=O), 6.85, 6.89 (sh), 7.1, 7.2 (sh), 7.25, 7.4, 7.8, 8.35, 8.65, 8.85, 9.35, 9.5, 9.8, 14.0 μ (broad); nmr δ 1.0 (d, J = 6 Hz, 3 H, CH_3CH), 1.1–2.2 (m, 24 H, with s at 1.32), 2.32 (m, 3 H, $CHCOCH_2$).

Anal. Calcd for $C_{16}H_{30}O$: *m/e* 238.2296. Found: *m/e* 238.2295.

Cyclopentadecanone (Exaltone, 19).—Bromine (10.24 g, 0.064 mol) was added dropwise to a solution of cyclohexadecanone **17** (8.2 g, 0.032 mol) in anhydrous ether (45 ml) at 5°. The reaction mixture was poured over ice water (45 g), benzene (25 ml) was then added, and the organic layer was separated. The aqueous layer was extracted with benzene. The combined benzene extract was washed with saturated solution of sodium bicarbonate and a saturated solution of sodium chloride until neutral, dried ($MgSO_4$), and on removal of solvent yielded 12.8 g (yield 96.2%) of crude dibromide. Without further purification and characterization the solution of crude dibromide (12.5 g) in anhydrous benzene (10 ml) was slowly added to the suspension of sodium methoxide (5.68 g, 0.105 mol) in anhydrous benzene (50 ml) over 20 min at 25–30°. Stirring was followed for an additional 15 min at 25°. The reaction mixture was poured into ice–water (50 g) and the organic layer was separated. The aqueous layer was extracted with benzene. The combined benzene extract was washed first with 5% hydrochloric acid solution and then with a saturated solution of sodium chloride, dried ($MgSO_4$), and on removal of solvent yielded 12.1 g of crude 1-carboxymethyl-1-cyclopentadecene (**18**). Pure material was isolated by glc (Carbowax 20M). The mass spectrum of **18** showed molecular ion peak at *m/e* 266 and other major peaks at *m/e* 41, 55, 81, 67, 95; ir (neat) 3.45, 3.54, 5.85 (C=CCOOCH$_3$), 6.15, 6.9 (sh), 7.0, 7.3, 7.45, 7.6, 8.15 (sh), 8.25 (sh), 8.4, 8.7, 9.8, 12.35 (broad), 13.55, 14.1 μ.

Anal. Calcd for $C_{17}H_{30}O_2$: *m/e* 266.2245. Found: *m/e* 266.2247.

Without further purification the unsaturated ester **18** (11.24 g, 0.04 mol) was added to concentrated sulfuric acid (25 ml) at

0° under nitrogen. After the addition was completed, chloroform (25 ml) was added and the temperature was raised to 35°. Sodium azide (3.12 g, 0.048 mol) was added in small portions at 35–40° over 20 min, and the mixture was stirred for additional 15 min. The reaction mixture was cooled to 25° and poured into ice–water (100 g), after which the whole mixture was steam distilled to obtain 3 l. of distillate. The distillate was saturated with solid sodium chloride and extracted with ether. The extract was washed with saturated sodium chloride solution, dried, and upon evaporation of solvent yielded 6.7 g yellow solid which was crystallized from petroleum ether (bp 30–60°) to obtain 6 g (yield 77.8%) of exaltone (**19**), mp 61–62°. Ir and mass spectrum were superimposable with those spectra of the authentic sample.

17-Oxobicyclo[14.1.0]heptadecane (13).—A solution of monoepoxide **2** (5 g) in methanol (100 ml) was hydrogenated under normal temperature and pressure using 10% palladium on carbon (1.5 g) as a catalyst. After usual work-up 5 g of solid saturated epoxide **13** (mp 33–35°) was obtained. Glc (Carbowax 20M) showed two peaks. The mass spectrum of the mixture of two isomers showed molecular ion peak at *m/e* 238 and other major peaks at *m/e* 55, 41, 82, 69, 67, 95; ir (neat) (mixture of two isomers) 3.42, 3.5, 6.87, 7.25, 7.3, 7.8, 7.95, 8.95, 9.4, 10.9, 11.25, 11.9, 12.9, 13.5, 14.0 μ (after 7.95 μ all bands were weak); nmr δ 1.35 (m with a s at 1.35, internal methylene), 2.46 (m, 1 H, epoxy CH), 2.7 (b, 1 H, epoxy CH).

Reaction of Saturated Epoxide 13 with Lithium Diethylamide.—To an ice-cold solution of diethylamine (8 g, 0.1 mol) in anhydrous ether (3.50 ml), 15% commercial butyllithium in hexane (62.5 ml, 0.1 mol) was added under a nitrogen atmosphere. After 10 min, a solution of **13** (10 g, 0.042 mol) in anhydrous ether (50 ml) was added, stirred for 1 hr at room temperature, and then refluxed for 51 hr. The reaction mixture was cooled and poured into ice-cold water, and the organic layer was separated. The aqueous layer was saturated with solid sodium chloride and extracted with ether, and the combined organic layers were washed with 50% sodium chloride solution and dried (Na_2SO_4). Evaporation of solvent yielded 9.4 g of material which was chromatographed on silicic acid (130 g)–hexane eluted 0.5 g (yield 5.4%) of 1,3-cyclohexadecadiene **14**; 10% ether in hexane eluted 6.2 g of mixture of epoxide **13** and 2-*trans*-cyclohexadecen-1-ol (**15**); 50% ether in hexane eluted another 2.6 g of pure alcohol **15**. The mixture of **13** and **15** (6.2 g) was rechromatographed on silicic acid (150 g)–5% ether in hexane eluted 2.5 g (25%) of epoxide **13**; and 10% ether in hexane eluted 3.6 g of alcohol **15**. The total amount of **15** thus obtained was 6.2 g (yield 62%). Glc of **15** showed one peak whose mass spectrum showed molecular ion at *m/e* 238 and other major peaks at *m/e* 41, 55, 57, 83, 43, 70; ir (neat) 3.0 (OH), 3.5, 6.02, 6.9, 6.95 (sh), 7.1, 7.3, 7.45, 7.75, 8.5, 8.7, 8.95, 9.4, 9.85 (C=CCHOH), 10.1, 10.35 (strong, trans CH=CH), 11.9, 12.7, 13.8 μ (broad); nmr δ 2.08 (b, 2 H, CH_2C=C), 2.88 (s, 1 H, OH), 3.96 (b, 1 H, CHO), 5.4 (m, 2 H, CH=CH).

Anal. Calcd for $C_{16}H_{30}O$: *m/e* 238.2296. Found: *m/e* 238.2300.

The mass spectrum of **14** showed a molecular ion peak at *m/e* 220 and other major peaks at *m/e* 80, 41, 67, 81, 82, 68; ir (neat) 3.35 (very weak), 3.45, 3.51, 5.95 and 6.05 (very weak), 6.9, 7.3, 7.45, 7.75, 8.15, 9.3, 10.15, and 10.35 (strong, broad, trans CH=CH), 13.9 μ (weak, broad); nmr δ 1.35 (strong s, internal methylene H), 2.11 (diffused q, 4 H, CH_2C=CC=C-CH), 5.26–6.5 (m, 4 H, CH=CHCH=CH).

Anal. Calcd for $C_{16}H_{28}$: *m/e* 220.2190. Found: *m/e* 220.2189.

Reaction of Saturated Epoxide 13 with Butyllithium.—Epoxide **13** (28 g) was treated with 15% butyllithium (75 ml) exactly as in the case of **2**. After usual work-up and column chromatography obtained were 15.2 g (yield 54.2%) of **17** (mp 58–60°, undepressed with the authentic sample) and 5.3 g (yield 18.9%) of **15**.

2-Cyclohexadecen-1-one (16).—Alcohol **15** (6 g) was oxidized with a solution of chromium trioxide in the same way as in the case of compound **3**. After usual work-up and column chromatography, there was obtained 4.2 g (yield 70%) of ketone **16**. The mass spectrum showed the molecular ion peak at *m/e* 236 and other major peaks *m/e* 55, 41, 81, 96; ir (neat) 3.35, 3.45, 3.52, 5.88 and 5.94, sh of 6.02 (C=CCO), 6.2, 6.9, 6.98, 7.29, 7.35, 7.45, 7.89, 8.3, 8.75, 8.95, 10.25 (strong, trans CH=CH), 11.3, 13.95 μ; nmr δ 1.28 (strong s, internal methylene H), 1.6 (broad m), 2.4 (m, 4 H, CH_2C=CCOCH_2), 5.94–6.10 (d, 1 H) and 6.50–6.80 (m, 1 H, CH=CHC=O).

Anal. Calcd for $C_{16}H_{28}O$: *m/e* 236.2140. Found: *m/e* 236.2135.

3-Methylcyclohexadecanone (7).—The ethereal (80 ml) solution of **16** (4 g) was treated with methylmagnesium bromide (7.2 ml) in the presence of cuprous chloride (0.11 g) exactly as in the case of **5**. After usual work-up and column chromatography obtained was 3.5 g (yield 80%) of **7**.

Autoxidation of 1,9-Cyclohexadecadiene (1).—Air was passed through a test tube containing 1,9-cyclohexadecadiene **1** (5 g) at 60–65°. After every 24 hr the oxidation was followed by glc. After 114 hr of passing air, an appreciable amount of oxygenated products was formed. The material became viscous and weighed 6.8 g. Glc (Carbowax 20M) of this autoxidized material indicated the formation of four isomeric monoepoxides (four peaks, 13%), whose ir and mass spectra were superimposable with the spectra of the four epoxides **2** formed by the epoxidation of 1,9-cyclohexadecadiene **1**, and two α,β-unsaturated ketones (two peaks, 9%), whose ir and mass spectra were superimposable with the spectra of the two ketones **5** obtained by the chromium trioxide oxidation of alcohol **4**.

Registry No.—*cis,cis*-**2**, 31446-71-6; *trans,trans*-**2**, 31446-72-7; *cis,trans*-**2**, 31489-81-3; *trans,cis*-**2**, 31446-73-8; *trans,trans*-**3**, 31489-82-4; *trans,cis*-**3**, 31446-74-9; *trans,trans*-**5**, 31446-75-0; *trans,cis*-**5**, 31446-76-1; *trans*-**6**, 31446-77-2; *cis*-**6**, 31446-78-3; **7**, 31446-79-4; **8**, 31446-80-7; **9**, 31446-81-8; **10**, 31446-82-9; **11**, 956-82-1; **12**, 22460-48-6; *cis*-**13**, 31446-85-2; *trans*-**13**, 31446-86-3; **14**, 31489-83-5; **15**, 31446-87-4; **16**, 31446-88-5; **17**, 2550-52-9; **18**, 31446-90-9; **19**, 502-72-7.

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Resin Acids. XXI.[1,2] Synthesis of Methyl Podocarp-8(14)-en-13-on-15-oate from the Levopimaric Acid–Formaldehyde Adduct

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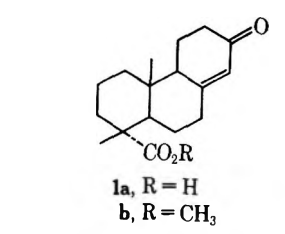
The transformation of the readily available levopimaric acid–formaldehyde adduct **3a** to the title compound **1b** by a convenient five-step sequence is described. Four of the steps proceed in quantitative or nearly quantitative yield. The first step involves an unusual oxidation of a cyclic ether to a δ lactone in the presence of a secondary hydroxyl group. In the last step three reactions, reductive elimination of an acetoxy group, β elimination of an acyloxy function, and decarboxylation, are effected at once.

The distribution of functional groups in (+)-podocarp-8(14)-en-13-on-15-oic acid (**1a**) makes this substance an attractive and potentially important starting material or relay for the synthesis of di- and triterpenoids. While the original method of preparation of **1a** by controlled ozonolysis of neoabietic acid (**2**)[3,4] as improved recently[5] is more convenient[6] than multistep routes[6,7] departing from dehydroabietic acid, studies on the use of **1a** have nevertheless been severely hampered by the relative scarcity of neoabietic acid whose isolation from pine gum or rosin in the requisite amounts is quite laborious.[8]

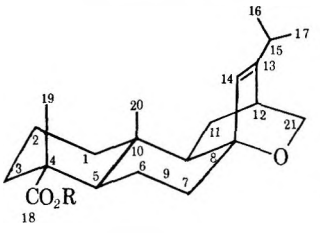
The levopimaric acid–formaldehyde adduct **3a** can be obtained very conveniently and in good yield from pine oleoresin.[9] It occurred to us that **3a** represented a potential precursor of **1a** if it could be transformed in good yield to **4**. The latter possesses the appropriate functionalities for an acid- or base-catalyzed cleavage to **5** which in turn could conceivably undergo a retro-aldol reaction to **1a**. In the following we describe the realization of our goal, albeit by a route which differs somewhat from the one envisioned originally.

Our previous experience with Diels–Alder adducts of levopimaric acid[10–12] indicated that reagent approach to the double bond of **3a** would, for steric reasons, occur from the side of the oxymethylene bridge and that oxymercuration–demercuration[13] would therefore result in the alcohol **6** by the mechanism suggested[14] for cis-oxymercuration of those olefins where back-side attack by an external nucleophile, and hence trans addition, is inhibited.[15] β elimination of the elements of water from **6** or an appropriate derivative should result in the isopropylidene compound **7** rather than

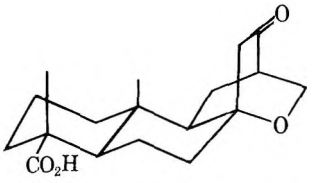


1a, R = H
b, R = CH_3

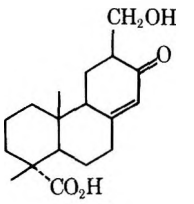
2



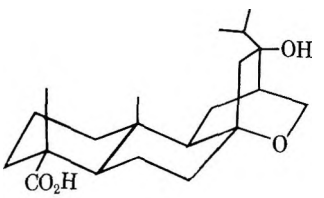
3a, R = H
b, R = CH_3



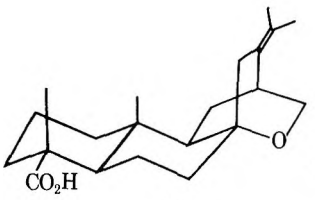
4



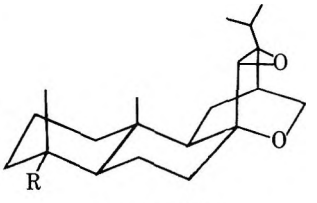
5



6



7



8a, R = CO_2H
b, R = CO_2CH_3
c, R = CH_2OH

3a because of the steric hindrance offered to attack of base on the bridge hydrogen trans to the hydroxyl group. Subsequent ozonolysis of **7** would furnish **4**.

In the event, **3b** was recovered unchanged from treatment with mercuric acetate–THF–H_2O although epoxidation proceeded normally to give **8b**. The stereochemistry assigned to this substance is based on analogy[11,12] and on the chemical shift (0.8 ppm) of the angular methyl group which would be expected to be more deshielded in the alternative arrangement with the oxygen atom oriented toward the C-10 methyl group. Acid-catalyzed ring opening of such epoxides does not produce glycols but 14 ketones for steric reasons that have been discussed previously;[11,12] similarly, treatment of **8b** with excess lithium **alumi-**

(1) Previous paper: W. Herz, R. C. Ligon, H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **35**, 3338 (1970).

(2) Supported in part by a grant from the National Science Foundation (GP-12582).

(3) G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.*, **70**, 339 (1948).

(4) W. M. Hoehn, U. S. Patent 2,682,555.

(5) S. W. Pelletier, K. N. Iyer, and C. W. J. Chang, *J. Org. Chem.*, **35**, 3535 (1970).

(6) A. W. Burgstahler and L. R. Worden, *J. Amer. Chem. Soc.*, **86**, 96 (1964).

(7) E. Wenkert, R. W. J. Carney, and C. Kaneko, *ibid.*, **83**, 4440 (1961).

(8) V. M. Loeblich and R. V. Lawrence, *J. Org. Chem.*, **21**, 610 (1956).

(9) B. A. Parkin, Jr., and G. W. Hedrick, *ibid.*, **30**, 2356 (1965).

(10) N. Halbrook, R. V. Lawrence, R. L. Dressler, R. C. Blackstone, and W. Herz, *ibid.*, **29**, 1017 (1964).

(11) W. Herz, R. N. Mirrington, H. Young, and Y. Y. Lin, *ibid.*, **33**, 4210 (1968).

(12) W. Herz and R. C. Blackstone, *ibid.*, **34**, 1257 (1969).

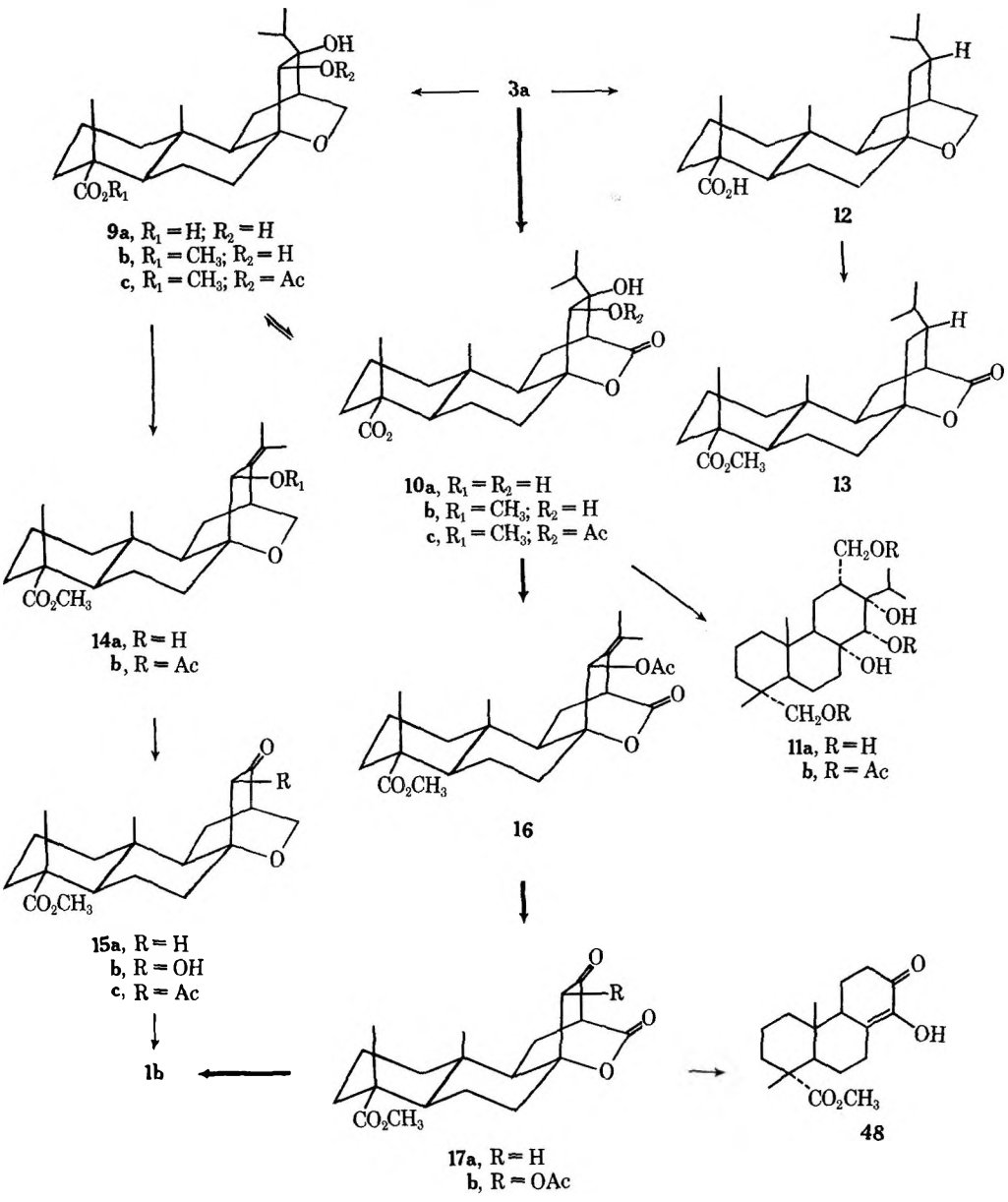
(13) The acid sensitivity of the adduct **3a** precluded adoption of more conventional hydration techniques.

(14) T. G. Traylor and A. W. Baker, *J. Amer. Chem. Soc.*, **85**, 2746 (1963); T. G. Traylor, *ibid.*, **86**, 244 (1964).

(15) Diels–Alder adducts of levopimaric acid fulfil this requirement.[11,12,16]

(16) N. Langlois and B. Gastambide, *Bull. Soc. Chim. Fr.*, 2966 (1965).

SCHEME I



num hydride produced only **8c** without affecting the oxide ring due to steric interference with nucleophilic attack from the rear. A different approach to **4** was therefore sought.

$KMnO_4$ oxidation of **3a** gave, after methylation with diazomethane, two substances, A and B. Limiting the amount of oxidizing agent[17] resulted in sole formation of more polar material A; treatment of **3a** with excess $KMnO_4$ or further oxidation of A resulted in quantitative conversion to the less polar substance B.

Structure **9b** (Scheme I) was assigned to A on the following grounds. The ir spectrum showed two hydroxyl bands and one carbonyl frequency at 1720 cm^{-1} associated with the ester function. In the nmr spectrum the broadened singlet of **3b** at 5.79 ppm due to the vinyl proton had been replaced by a sharp singlet at 3.48 ppm assignable to H-14, now geminal to a hydroxyl group. The C-10 methyl signal exhibited a normal chemical shift (0.90 ppm) instead of being characteristically shielded as in the precursor **3b**, but the two broadened doublets of the oxymethylene protons at 4.26 and 3.66 ppm had been retained. Formation of an acetonide established that the two hydroxyl groups were vicinal and cis. Since the acetonide and the cyclic manganate ester involved[18] in formation of a glycol possess large steric requirements, it could be surmised that only that glycol had been formed in which the hydroxyl groups were oriented toward the oxymethylene bridge, *i.e.*, **9b**. In the other arrangement, the C-10 methyl resonance should be deshielded by the 14-hydroxyl group; this was not observed.

Compound B also possessed two hydroxyl groups, one of which was strongly bonded intramolecularly, and two carbonyl groups (ir bands at 1720 and 1760 cm^{-1}). The second of these frequencies was attributed to a strained δ-lactone function as shown in **10b**, since

(17) The amount of $KMnO_4$ necessary to convert **3a** to **9b** or to **10b** exclusively was approximately 50% more than that calculated on the basis of complete reduction of Mn^{+7} to MnO_2 but corresponded approximately to reduction to Mn^{+6}. Consumption of oxidizing agent through conversion of **3a** or **9b** to a ketol (*cf.* R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, New York and Amsterdam, 1964, p 60) was not a factor.

(18) K. B. Wiberg and K. A. Saegebarth, *J. Amer. Chem. Soc.*, **79**, 2822 (1957).

the nmr spectrum lacked the peaks of the oxymethylene bridge but displayed a sharp one-proton signal at 4.2 ppm (H-14) and a one-proton doublet of doublets at 3.24 ppm (H-12, α to the lactone function). The proposed chemical relationship between **9b** and **10b** was demonstrated by reduction of **10b** to **9b** with the $NaBH_4$–BF_3 reagent. Lithium aluminum hydride reduction of **10b** gave a noncrystalline pentol **11a** which was characterized as the triacetate **11b**.

The formation of lactones from cyclic ethers by $KMnO_4$ oxidation has not to our knowledge been observed previously. The presence of the hydroxyl groups of **9b** is not responsible for this unusual oxidation reaction since $KMnO_4$ treatment of **12** followed by methylation gave a 60% yield of **13**. Presumably, by analogy with $KMnO_4$ oxidation of hydrocarbons,[19] permanganate ion abstracts a hydrogen atom from the oxymethylene group of **9a** or **12** and gives a radical pair which is trapped momentarily in the solvent cage. Recombination yields a hypomanganate ester which undergoes hydrolysis to a hemiacetal. Further oxidation of the latter affords **10a** and **13**. However, it is difficult to understand why oxidation of **9** and **12** should proceed so much more readily than that of ordinary ethers.

The observation that the secondary hydroxyl groups of **9a**, **9b**, **10a**, and **10b** were not affected by basic $KMnO_4$ while oxidation of the ether to a lactone, presumably a more difficult reaction, took place readily is worthy of comment. Other basic oxidizing agents were equally ineffective in attacking the secondary hydroxyl group of **9b** or **10b**,[20] presumably because its oxidation would require hydride abstraction in an extremely hindered environment. On the other hand, oxidation of similar, 14-hydroxy derivatives has been readily accomplished with chromic oxide in an acidic medium;[11,12] this reagent could not be tested in the present instance because of acid sensitivity of the oxymethylene bridge.

Treatment of **9b** with thionyl chloride–pyridine resulted in formation of a sulfite rather than in the hoped for elimination of the tertiary hydroxyl group. Protection of the secondary hydroxyl group prior to dehydration seemed therefore necessary and was effected by quantitative conversion of **9b** to the acetate **9c**.[21] Subsequent exposure to thionyl chloride–pyridine afforded a quantitative yield of **14b** which possessed the requisite spectral properties (downfield shift of the now allylic H-14 to 5.8 ppm, appearance of a complex one-proton signal at 2.73 ppm attributable to newly-allylic H-12, two vinyl methyl resonances) and was hydrolyzed to **14a** with dilute methanolic KOH. Ozonolysis of **14a** (ethyl acetate, −78°) and decomposition of the ozonide with dimethyl sulfide[22] furnished the ketol **15b** (54%) which was somewhat unstable. Ozonolysis of **14b** resulted in considerable improvement and gave a quantitative yield of noncrystalline **15c** which was characterized as the 2,4-dinitrophenylhydrazone.

Removal of the isopropyl group from the adduct **3a** had thus been accomplished in excellent overall yield. To achieve the cleavage reaction envisioned earlier without introducing complications, it was first necessary to remove the functional group at C-14. Attempts to effect reductive elimination of the acetoxy group with combinations of zinc and acetic acid, acetic anhydride, and formic acid or with calcium–liquid ammonia were frustrated by formation of polymeric material. Treatment of **15c** with chromous chloride resulted in a complex mixture which was refluxed with methanolic sodium hydroxide in an effort to convert **15a**, shown to be present by nmr analysis, to the desired enone **1b**. Analysis of the product indeed established the presence of **1b**, but the estimated yield was only 10–15%.

Lactone **10b** was now subjected to the reaction sequence which had been used successfully for deisopropylating **9b**, since it was hoped that the lactone analog **17** might be cleaved under the acid conditions of the chromous chloride reduction and might then be induced to decarboxylate fairly readily. This expectation was realized. Acetylation of **10b** to **10c** and dehydration of the latter to **16** proceeded in quantitative yield. Ozonolysis of **16** (ethyl acetate, −78°) followed by dimethyl sulfide work-up gave a 95% yield of the relatively unstable ketoacetate **17b** which could not be induced to crystallize but possessed spectral properties (sharp one-proton peak at 5.52 ppm due to H-14, broadened one-proton doublet at 3.5 ppm due to H-12, acetate singlet, two methyl singlets, and no vinyl methyl resonances) consonant with the assigned structure.

Attempts to remove the acetate function of **17b** reductively with zinc–acetic acid or calcium–liquid ammonia again yielded only polymeric material. When, on the other hand, a solution of **17** in tetrahydrofuran was refluxed with chromous chloride, chromatography of the crude product gave two crystalline compounds. The first, isolated in 40% yield, was indeed the desired **1b**; the second (20%) was the diosphenol **18** which has recently been encountered[23] as a transformation product of **1b**.

Formation of **1b** and **18** from **17b** can be rationalized as follows. Under the influence of the acidic reagent the normal reduction product **17a** undergoes β elimination of the lactone function to give the β-keto acid **19** which undergoes decarboxylation to **1b**. Formation of **18** is the result of acetate hydrolysis[24] and lactone cleavage prior to reductive elimination. Mild conditions should suppress this side reaction and, indeed, when the reduction was carried out at room temperature only **1b** was formed. However, the reaction proceeded only slowly at room temperature; after 1 week, the yield of **1b** did not exceed 40%. Nevertheless, since each of the preceding four steps **3** → **10a** → **10b** → **16** → **17b** proceeds in excellent yield, the new

(19) K. Wiberg, Ed., "Oxidation in Organic Chemistry," Academic Press, New York and London, 1965, p 37.

(20) Attempted oxidation of **9b** or **10b** with Sarett, Cornforth, and Collins reagent resulted in recovery of starting material. Use of Jones reagent gave complex mixtures due to acid-catalyzed ether cleavage.

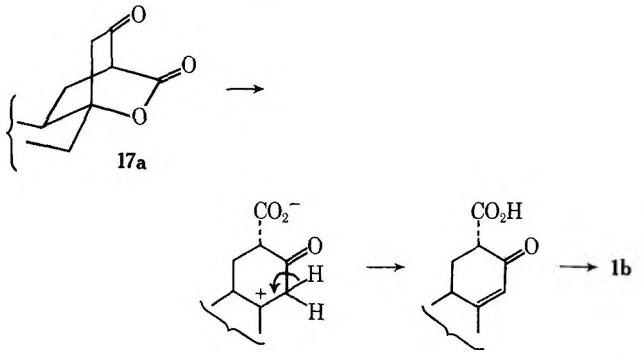
(21) The nmr spectrum of this substance (see Experimental Section) exhibited slight deshielding of the C-10 methyl group and some shielding of one of the methyls of the isopropyl group, indicating slight distortion of the C-13–C-14 bridge toward ring A probably due to dipolar interaction between the ether oxygen and the acetate function.

(22) J. J. Pappas, W. P. Keaveney, E. Grancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

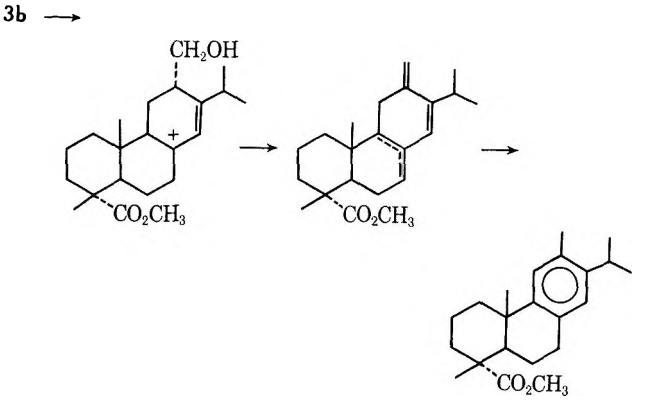
(23) S. W. Pelletier, C. W. J. Chang, and K. N. Iyer, *J. Org. Chem.*, **34**, 3477 (1969).

(24) As monitored by nmr spectroscopy, the initial step in the decomposition of **17b** prior to formation of intractable material is hydrolysis of the acetate function.

route to **1b** represents a useful alternative to its preparation from neoabietic acid.

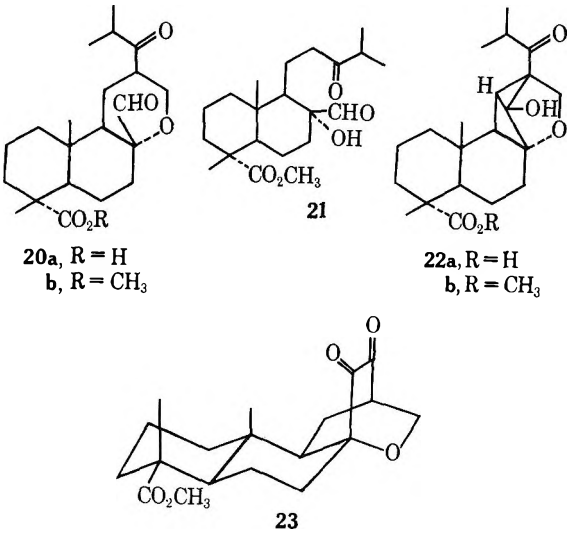


In the following, we briefly describe several other transformations of **3** or its derivatives which possess features of interest. In an attempt to introduce halogen at an allylic position with a view toward eventual removal of the isopropyl side chain, **3b** was refluxed with *N*-bromosuccinimide in benzene. This resulted not in substitution but in formation (90–95% yield) of methyl 12-methyldehydroabietate (**19**).[25] The same substance was obtained in practically quantitative yield by refluxing the adduct with iodine or *p*-toluenesulfonic acid in benzene, presumably by the path indicated below.[26]



Cleavage of the C-13,C-14 double bond of **3a** by ozonolysis[11,12] resulted in the formation of a complex mixture from which the ketoaldehyde **20** was isolated in low yield. A much better route to this substance was oxidation of **9a** with sodium metaperiodate. Acid treatment of **20** in an attempt to effect a retroaldol cleavage to **21** was unproductive; dilute base resulted in aldol condensation to **22** rather than retro-aldol reaction, as indicated by the nmr spectrum (H-14 at 4.10, H-15 at 4.16 and 3.74, H-16 at 2.98 ppm). Since the resonance of the C-10 methyl group at 0.91 ppm was not deshielded, the hydroxyl group of **22** is oriented toward the oxymethylene bridge. Efforts to utilize **20** and **22** for further studies are described in the Experimental Section.

In one run involving chromous chloride reduction of **15c**, the reaction mixture was accidentally exposed to the atmosphere. Quenching of the reaction after several hours resulted in a 65% yield of **23**. In an attempt to determine the nature of the oxidizing agent, addition of chromic chloride without prior reduction to chromous chloride also effected conversion of **15c** to **23**. The nature of the reagent responsible for this unexpected oxidation of a ketol to a diketone is currently under investigation.



Experimental Section[27]

Epoxidation of 3b.—A solution of 2.0 g of **3b**, prepared as described[9] from **3a**,[28] and 1 g of *m*-chloroperbenzoic acid was stirred for 18 hr at room temperature and then washed several times with 5% KI solution, sodium thiosulfate solution, and water. The dried organic layer was evaporated at reduced pressure. The residue was taken up in ether and the ether extract washed, dried, and evaporated. The crystalline residue of **8b**, wt 2.1 g, was recrystallized from hexane and had mp 109–111°; ir bands at 1720 and 1230 cm^{-1} (ester); nmr signals at 3.94 and 3.52 (m, H-21), 3.62 (methoxyl), 3.12 (H-14), 1.17 (C-4 methyl), 0.80 (C-10 methyl), 1.06 and 0.78 ppm (d, J = 7 Hz, isopropyl methyls); $[\alpha]^{22}D$ +64.5° ($CHCl_3$).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45; O, 17.66. Found: C, 72.47; H, 9.44; O, 18.11.

Lithium aluminum hydride reduction of 1 g of **8b** in 30 ml of THF in the usual fashion gave, after acid hydrolysis and isolation of the product in the usual manner, 0.8 g of a gum which could not be induced to crystallize. The nmr spectrum indicated that the epoxide ring had been retained (H-14 signal at 3.12 ppm) but that the ester function had been reduced.

$KMnO_4$ Oxidation of 3a. A.—To a solution of 10 g of **3a** in 50 ml of 3% NaOH solution was added dropwise with stirring 4.5 g of $KMnO_4$[29] in 50 ml of water. Stirring was continued for an additional 15 min, following which the contents were mixed with a solution of 5 g of hydroxylamine hydrochloride in 50 ml of water. Addition of concentrated HCl, filtration, and washing with water gave 6.7 g of solid **9a** which was recrystallized from methanol–water and then melted at 279°.

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35; O, 21.83. Found: C, 68.88; H, 9.12; O, 22.22.

Methylation of **9a** with diazomethane gave **9b**, identical in all respects with a sample isolated from the mixture as described below.

B.—Oxidation of 10 g of **3a** in 50 ml of 4% sodium hydroxide solution with 10 g of $KMnO_4$ in 100 ml of water in the manner described above gave 9.2 g of solid product which was dissolved in chloroform–methanol and methylated with ethereal diazomethane. Removal of solvent gave 9.3 g of solid material which on tlc showed two spots of very similar R_f value. The material was extracted with three 20-ml portions of benzene–acetone (4:1). The residue **10b**, wt 1.5 g, was homogeneous on

(25) D. K. Black and G. W. Hedrick, *J. Org. Chem.*, **32**, 3758 (1967).

(26) In the case of the NBS reaction the acid catalyst may be the HBr contaminant usually present in commercial samples or may be produced by allylic substitution and spontaneous dehydrohalogenation.

(27) For details concerning methods, see W. Herz and J. Schmid, *J. Org. Chem.*, **34**, 3464 (1969), footnote 52.

(28) We would like to thank Dr. Glen W. Hedrick, Naval Stores Laboratory, Olustee, Fla., for a generous supply of the adduct **3a**.

(29) Use of less $KMnO_4$ resulted in formation of a mixture of **3a** and **9a**.

tlc. Evaporation of the extracts gave 6.7 g of a mixture which was dissolved in 10 ml of benzene–acetone (4:1) chromatographed over 100 g of F-20 alumina and eluted with benzene–acetone (4:1). The less polar fractions contained an additional 1.7 g of **10b**; the latter fractions eluted 6 g of **9b**.

Recrystallization of **9b** from methanol gave material which had mp 182–184°; $[\alpha]^{27}D$ +80.0° (EtOH); ir bands at 3520 and 3500 (hydroxyls) and 1720 cm^{-1} (ester); nmr signals at 4.27 and 3.67 (m, H-21), 3.7 (methoxyl), 3.48 and 2.98 (OH, exchangeable with D_2O), 1.18 (C-4 methyl), 0.9 (C-10 methyl), 0.93 and 0.97 ppm (d, J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54; O, 21.20. Found: C, 69.09; H, 9.44; O, 21.17.

Recrystallization of **10b** from methanol gave needles which had mp 279°; $[\alpha]^{27}D$ +43.5° ($CHCl_3$); ir bands at 3520 and 3340 (OH), 1760 (δ lactone), and 1720 cm^{-1} (ester); nmr signals (pyridine-d_5) at 5.84 and 4.48 (OH), 4.1 (H-14), 3.72 (methoxyl), 3.28 (m, H-12), 1.19 (C-4 methyl), 0.91 (C-10 methyl), 1.13 and 1.10 ppm (d, J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.34. Found: C, 66.69; H, 8.77; O, 24.19.

C.—Oxidation of 5 g of **3a** with 10 g of $KMnO_4$ and methylation of the product with CH_2N_2 gave 4.5 g (75%) of recrystallized **10b**.

Acetonide of 9b.—A mixture of 0.5 g of **9b**, 30 ml of anhydrous acetone, and 0.2 ml of 70–80% $HClO_4$ solution was stirred overnight and diluted with water. The precipitated acetonide was recrystallized from methanol (yield quantitative) and had mp 155–157°; ir band at 1720 cm^{-1} (ester); nmr signals at 4.16 (H-14), 4.16 and 3.67 (m, H-21), 3.73 (methoxyl), 1.62 and 1.55 (methyls of acetonide), 1.18 (C-4 methyl), 1.05 and 1.00 (d, J = 7 Hz, isopropyl methyls), 0.87 ppm (C-10 methyl).

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.32; H, 9.73; O, 18.99.

Sulfite of 9b.—Treatment of 0.5 g of **9b** in 2 ml of pyridine with 0.5 ml of thionyl chloride overnight in an atmosphere protected from moisture and decomposition by pouring over ice gave a solid. Recrystallization from methanol afforded the sulfite which had mp 137–138°; no hydroxyls in ir spectrum; nmr signals at 4.36 (H-14), 4.25 and 3.75 (m, H-21), 3.68 (methoxyl), 1.18 (C-4 methyl), 1.12 and 0.9 (d, J = 7 Hz, isopropyl methyls), 0.84 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{34}O_6S$: C, 62.06; H, 8.00; O, 22.55; S, 7.29. Found: C, 62.00; H, 7.98; O, 22.55; S, 7.50.

Hydrolysis of the sulfite with 5% NaOH solution at room temperature for 6 hr followed by acidification regenerated **9b** in quantitative yield.

Oxidation of 9a.—Oxidation of 5 g of **9a** with 6 g of $KMnO_4$ and methylation of the product with CH_2N_2 gave 5.25 g (~100%) of recrystallized **10b**.

Reduction of 10b. A.—A solution of 1 g of **10b** and 21 g of boron trifluoride etherate in 30 ml of anhydrous ether was added dropwise with cooling and stirring to 0.38 g of $NaBH_4$ in 15 ml of diglyme. The mixture was refluxed for 1 hr after the addition was complete, chilled, stirred with 10 ml of 37% H_2O_2 and 10 ml of 2% NaOH solution, and extracted with ether. The organic extract was washed, dried, and evaporated. The gummy residue was triturated with methanol and deposited 0.5 g of pure **9b**.

B.—Reduction of 1 g of **10b** in 20 ml of tetrahydrofuran with 1 g of $LiAlH_4$ in 20 ml of tetrahydrofuran in the usual manner, acid hydrolysis after stirring overnight, extraction with ether, and purification in the usual fashion gave 1 g of crude **11a**. This was dissolved in 3 ml of pyridine and stirred with 4 ml of acetic anhydride overnight. Chromatography of the product over silica gel and elution with benzene afforded **11b** which was recrystallized from hexane and had mp 147–148°; ir bands at 3580 and 3450 (OH) and 1745–1720 cm^{-1} (ester and three acetates); nmr signals at 5.17 (H-14), 4.7–3.5 (c, 5 protons, H-14, H-18, and H-21), 2.18, 2.02, 2.01 (3 acetates), 1.05 (C-4 methyl), 0.85 (C-10 methyl), 0.97 and 0.96 ppm (d, J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{27}H_{44}O_8$: C, 65.30; H, 8.93; O, 25.77. Found: C, 65.57; H, 8.86; O, 25.58.

Oxidation of 12.—Oxidation of 1.5 g of the dihydroadduct **12**[9] with 1.5 g of $KMnO_4$ and work-up in the manner described for **9a** gave 1.5 g of a gummy residue which was esterified with diazomethane. Several recrystallizations afforded **13** in 60% yield: mp 164–165°; ir bands at 1745 (lactone) and 1720 cm^{-1} (ester); nmr signals at 3.67 (methoxyl), 2.7 (c, $W_{1/2}$ = 7 Hz, H-12), 1.18 (C-4 methyl), 1.00 (C-10 methyl), 0.94 and 0.92 ppm (d, J = 6 Hz, isopropyl methyls).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45; O, 17.65. Found: C, 72.53; H, 9.61; O, 18.18.

Preparation of 14b.—A solution of 20 g of **9b** in 30 ml of dry pyridine was stirred overnight at room temperature with 35 ml of acetic anhydride in an atmosphere protected from moisture, poured on ice, and extracted with ether. The organic layer was washed, dried, and evaporated. The residue was recrystallized from methanol–water and afforded, in essentially quantitative yield, **9c**, which had mp 147–148°; ir bands at 3520 (OH) and 1730–1720 cm^{-1} (acetate and carbomethoxy); nmr signals at 4.9 (H-14), 4.24 and 3.6 (m, H-21), 3.58 (methoxyl), 2.58 (OH), 2.12 (acetate), 1.13 (C-4 methyl), 1.00 (C-10 methyl), 0.90 and ppm (d, J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06; O, 22.72. Found: C, 68.25; H, 8.53; O, 22.75.

Dehydration of 10 g of **9c** in 20 ml of dry pyridine was effected by adding dropwise 2.5 ml of thionyl chloride with stirring and cooling and continuing the stirring for 20 min after addition was complete. The mixture was poured on ice and extracted with ether. The washed and dried ether extract was evaporated and afforded 9.8 g of **14b** sufficiently pure for further work. Recrystallization from pentane gave **14b** which had mp 138–139°; ir bands at 1735 (acetate) and 1720 cm^{-1} (carbomethoxy); nmr signals at 5.8 (H-14), 3.88 (c, $W_{1/2}$ = 7 Hz, H-12), 2.09 (acetate), 1.71 and 1.58 (vinyl methyls of isopropylidene), 1.13 (C-4 methyl), 0.80 ppm (C-10 methyl).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; O, 19.78. Found: C, 70.82; H, 8.92; O, 20.18.

Hydrolysis of 14b and Ozonolysis of 14a.—A mixture of 1 g of **14b** and 10 ml of 2% methanolic sodium hydroxide was stirred at room temperature. After 5 min the solid had dissolved completely and tlc showed complete disappearance of starting material. Stirring was continued for an additional 5 min, the solution was diluted with water, and the precipitated **14a** (yield quantitative) was recrystallized from methanol–water. It had mp 144–145°; ir bands at 3450 (OH) and 1720 cm^{-1} (carbomethoxy); nmr signals at 4.25 (d, J = 10 Hz, H-14, collapsed to singlet on addition of D_2O), 3.84 (c, ($W_{1/2}$ = 4 Hz, H-21), 3.67 (methoxyl), 2.8 (c, $W_{1/2}$ = 7, H-12), 2.27 (d, OH), 1.81 and 1.71 (isopropylidene), 1.12 (C-4 methyl), 0.70 ppm (C-10 methyl). Because the product had a tendency to decompose on standing it was not analyzed. Reacetylation of **14a** with acetic anhydride pyridine gave **14b** in quantitative yield.

A solution of 2 g of **14a** in 50 ml of methylene chloride was cooled to 0° and ozonized until excess ozone was detected in the KI trap. The solution was flushed with dry nitrogen to remove excess ozone, mixed with 1 ml of dimethyl sulfide, and stirred overnight. The solvents were removed at reduced pressure and the residue was taken up in ether. Repeated washing of the extracts, drying, and evaporation gave 1.8 g of a gummy residue. Tlc (benzene–methanol 9:1) showed one major and several minor spots. Chromatography over silica gel and elution with chloroform afforded 1 g of **15b** which was recrystallized from pentane–methylene chloride and had mp 160–162°; ir bands at 3420 (hydroxyl) and 1730 and 1720 cm^{-1} (carbomethoxy and ketone); nmr signals at 4.02 (H-14), 4.02 (c, $W_{1/2}$ = 4 Hz, H-21), 3.67 (methoxyl), 1.16 (C-4 methyl), 0.88 ppm (C-10 methyl).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39; O, 23.78. Found: C, 67.78; H, 8.53; O, 23.57.

Ozonolysis of 14b.—Ozonolysis of 1 g of **14b** in 20 ml of methylene chloride at acetone–Dry Ice temperature and work-up in the manner described in the previous paragraph gave 0.8 g of a gummy ketoacetate **15c**, which had a complex set of ir bands at 1745–1720 cm^{-1} and nmr signals at 5.57 (H-14), 4.1 (m, $W_{1/2}$ = 4 Hz, H-21), 3.7 (methoxyl), 2.56 (c, $W_{1/2}$ = 7 Hz, H-12), 2.20 (acetate), 1.18 (C-4 methyl), 1.01 ppm (C-10 methyl). The material decomposed on standing.

The 2,4-dinitrophenylhydrazone was recrystallized from methanol and melted at 179–181°.

Anal. Calcd for $C_{27}H_{34}N_4O_9$: C, 58.05; H, 6.14; N, 10.03. Found: C, 58.59; H, 6.28; N, 9.85.

To a solution of 2 g of **15c** in 30 ml of tetrahydrofuran in a flask protected from the atmosphere and swept with purified nitrogen was added with stirring 10 ml of aqueous chromous chloride solution from a Jones reductor.[30] The mixture was stirred overnight and extracted with chloroform. The organic extract was

(30) H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964).

washed, dried, and evaporated; although the gummy residue showed only one spot on tlc, the nmr spectrum revealed that it was a mixture of at least three components which could not be resolved ty tlc in various solvent systems. The crude product was therefore refluxed with 50 ml of 5% methanolic NaOH for 6 hr, concentrated at reduced pressure, diluted with water, and extracted with ether. The washed and dried ether extract yielded 1.5 g of a gummy residue which showed several spots on tlc one of which (10–15% of the mixture) corresponded to authentic **1b**.

Conversion of 10b to 1b.—A solution of 20 g of **10b** in 20 ml of pyridine was stirred overnight with 20 ml of acetic anhydridel Work-up in the manner described for 9c and recrystallization from hexane gave a quantitative yield of **10c** which had mp 203–205°; ir bands at 3560 (OH), 1760 (lactone), 1740 (acetate), and 1730 cm^{-1} (carbomethoxy); nmr signals at 5.3 (H-14), 3.73 (methoxyl), 3.09 (c, H-12), 2.83 (OH), 2.27 (acetate), 1.20 (C-4 methyl), 1.11 (C-10 methyl), 0.98 and 0.85 ppm (d, J = 7 Hz, isopropyl).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31; O, 25.66. Found: C, 66.03; H, 8.50; O, 25.27.

Dehydration of 1.0 g of **10c** with thionyl chloride–pyridine and work-up in the manner described for **14b** gave a quantitative yield of **16** which was recrystallized from methanol–water and had mp 144–145°; $[\alpha]^{22}D$ +33.2° ($CHCl_3$); ir bands at 1760 (lactone), 1740 (acetate), 1725 (carbomethoxy), and 1670 cm^{-1} (weak, double bond); nmr signals at 6.07 (br, $W_{1/2}$ = 4 Hz, H-14), 3.70 (methoxyl), 3.7 (c, H-12), 2.10 (acetate), 1.82 and 1.63 (vinyl methyls), 1.20 (C-4 methyl), 0.90 ppm (C-10 methyl).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19; O, 22.94. Found: C, 68.70; H, 8.16; O, 23.39.

Ozonolysis of 5 g of **16** in 30 ml of methylene chloride at −78° and work-up with dimethyl sulfide in the manner described for **14a** gave 4.5 g (96%) of gummy **17b** whose nmr spectrum had signals at 5.57 (H-14), 3.65 (methoxyl), 3.48 (c, H-12), 2.16 (acetate), 1.18 (C-4 methyl), 1.12 ppm (C-10 methyl). Since this material was unstable at room temperature in air and decomposed during attempts at tlc purification, it was used directly for further experiments.

To a solution of 4 g of **17b** in 40 ml of deoxygenated tetrahydrofuran was added with stirring in a nitrogen atmosphere 25 ml of 1 N chromous chloride solution. After 8 days, solvent was removed at reduced pressure and the residue was extracted thoroughly with chloroform. The combined washed and dried chloroform extracts were evaporated and the residual gum, wt 3.5 g, whose major component was **1b** (tlc analysis) was chromatographed over alumina. Elution with benzene gave **1b** in 40% yield, mp 126–127°, whose physical properties (melting point, rotation, ir and nmr spectra) were in agreement with the literature values.

When the reaction mixture was refluxed for 24 hr and worked up as described above, chromatography of the crude product afforded a 40% yield of **1b** and a 20% yield of **18**, mp 124° (lit.[22] mp 124–125°); ir and nmr spectra were in accord with those reported previously.[22]

Methyl 12-Methyl-8,11,13-abietatrien-18-oate (19).—A solution of 1.5 g of **3b** in 50 ml of dry benzene was refluxed with 0.7 g of N-bromosuccinimide, cooled, and washed thoroughly with water. The dried benzene was evaporated and the solid residue, wt 1.3 g, mp 107–109°, was recrystallized from methanol–water. It had mp 113°; ir bands at 1720 and 1250 cm^{-1} (ester); nmr signals at 6.91 (H-11), 6.82 (H.14), 3.6 (methoxyl), 2.22 (C-12 methyl), 1.22 (C-4 methyl), 1.18 (C-10 methyl), 1.16 ppm (d, J = 7 Hz, two isopropyl methyls) in agreement with the literature values.[25]

The same compound was obtained in quantitative yield by refluxing 1.5 g of **3b** in 50 ml of dry benzene with 0.2 g of iodine or with 0.1 g of p-toluenesulfonic acid.

Periodate Cleavage of 9a.—A solution of 5 g of **9a** in 50 ml of methanol, 2 g of sodium metaperiodate in 10 ml of water, and 1 ml of concentrated HCl was stirred for 6 hr, concentrated at reduced pressure to remove methanol, and diluted with water. The precipitate of **20a**, obtained in quantitative yield, was recrystallized from methanol–water and then had mp 179–180°; ir bands at 1745, 1735, and 1720 cm^{-1}; nmr signals at 9.90 (aldehydic proton), 3.78 (c, H-21), 1.17 (C-4 methyl), 1.05 (d, J = 7 Hz, isopropyl methyls), 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.34; H, 8.82; O, 22.07.

Methylation with diazomethane and recrystallization from gave the methyl ester **20b** which had mp 102–104°; nmr signals at 9.83 (aldehyde), 3.78 (c, H-21), 3.67 (methoxyl), 1.11 (C-4 methyl), 1.07 (d, J = 7 Hz, isopropyl methyls), 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05; O, 21.13. Found: C, 69.68; H, 9.17; O, 21.30.

Preparation of 22a.—A solution of 2 g of **20a** in 30 ml of 2% methanolic sodium hydroxide was stirred for 1 hr, concentrated to small volume at reduced pressure, and diluted with water. Recrystallization from acetone–hexane gave **22a** which had mp 248°; ir bands at 3440 (OH), 3320 (carboxyl OH), 1730 (acid), and 1700 cm^{-1} (ketone); nmr signals at 4.10 (H-14), 4.16 and 3.74 (m, H-21), 2.98 (hept, J = 6.5 Hz, H-15), 1.20 (C-4 methyl), 1.1 (d center of two doublets, J = 6.5 Hz, isopropyls), 0.92 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.30; H, 8.90; O, 22.08.

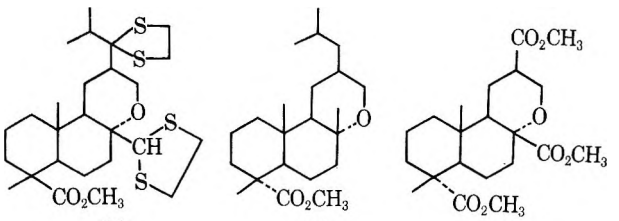
The ester **22b** was prepared by methylation of **22a** or by base treatment of **20b** and melted at 173°.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05; O, 21.13. Found: C, 69.75; H, 9.12; O, 21.25.

The ester **22b** was recovered quantitatively from an attempted reaction with m-chloroperbenzoic acid. Treatment of 2 g of **22b** with 3 ml of ethanedithiol and 0.5 ml of boron trifluoride etherate gave the gummy bisethylenedithiane derivative **24**, yield 1 g after preparative tlc (benzene–acetone 9:1), which had only one carbonyl absorption at 1720 cm^{-1} (ester) and nmr signals at 5.2 (H-14), 4.22 (m, H-21), 3.7 (methoxyl), 3.2 (br, $W_{1/2}$ = 3 Hz, 8 methylene protons α to S), 1.18 (C-4 methyl), 1.11 and 1.09 (d, J = 6 Hz, isopropyl methyls), 1.09 ppm (C-10 methyl). Attempts to restrict the reaction of **22b** with ethanedithiol to condensation with 1 mol equiv of dithiol were unsuccessful.

Desulfurization of 1 g of **24** in absolute methanol by refluxing with 10 g of Raney nickel for 18 hr, filtration, evaporation, and recrystallization of the solid residue from methanol–water gave a quantitative yield of **25** which had mp 62° and nmr signals at 3.72 (methoxyl), 3.57 (c, H-21), 1.22 (C-8 methyl), 1.18 (C-4 methyl), 0.90 and 0.86 (d, J = 6.5 Hz, isopropyl methyls), 0.80 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93; O, 13.69. Found: C, 75.10; H, 10.77; O, 13.95.



24 **25** **26**

Oxidation of 15c to 23.—A solution of 2 g of **15c** in 30 ml of tetrahydrofuran was mixed with 10 ml of the chromic chloride hexahydrate solution used for the preparation of chromous chloride with stirring. A white crystalline substance precipitated during this period. The mixture was diluted with water and filtered. Recrystallization from methanol–water gave a 65% yield of **23** which had mp 205–210°; a complex set of ir bands at 1730–1720 cm^{-1} (two ketones and ester); nmr signals at 4.0 and 3.73 (c, H-21), 3.66 (methoxyl), 1.17 (C-4 methyl), 0.92 ppm (C.10 methyl).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 67.83; H, 8.39; O, 23.78. Found: C, 67.77; H, 8.37; O, 23.68.

Oxidation of 1 g of **23** in 10 ml of methanol with 0.5 g of sodium metaperiodate in the manner described for the oxidation of **9b** gave a gum which was methylated by treatment with diazomethane and chromatographed over silica gel. Chloroform eluted 0.3 g of the homogeneous gummy triester **26** which had a complex ir band at 1730–1720 cm^{-1} (three carbomethoxyls) and nmr peaks at 3.88 and 3.66 (m, H-21), 3.63 (three methoxyls), 1.12 (C-4 methyl), 0.82 ppm (C-10 methyl).

Registry No.—**1b**, 5091-97-4; **8b**, 31579-57-4; **9a**, 31579-58-5; **9b**, 31579-59-6; **9b** acetonide, 31579-60-9;

9b sulfite, 31579-61-0; 9c, 31579-62-1, 10b, 31579-63-2; 10c, 31579-64-3; 11b, 31579-44-9; 13, 31579-65-4; 14a, 31579-66-5; 14b, 31579-67-6; 15b, 31579-45-0; 15c, 31579-46-1; 15 2,4-DNPH, 31579-47-2; 16, 31579-48-3; 17b, 31579-49-4; 20, 31579-50-7; 20b, 31579-51-8; 22a, 31579-52-9; 22b, 31579-53-0; 23, 31579-54-1; 24, 31579-55-2; 25, 31579-56-3; 26, 31579-68-7.

Steroids with Abnormal Internal Configuration. A Stereospecific Synthesis of 8α-Methyl Steroids[1]

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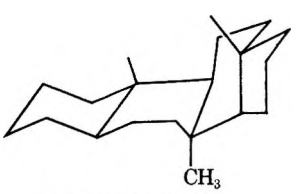
Stereospecific syntheses of 8α-methylcholestan-3β-ol-6-one acetate and 17-ethynyl-8α-methyltestosterone were accomplished. The synthetic scheme included a series of four reactions starting with steroid 5,7-dienes: hydroboration to the Δ⁷-6α-ol, Simmons–Smith addition to form the 7α,8α-methano-6α-ol, Jones oxidation, and lithium in ammonia reductive ring opening to form the 8α-methyl-6-one. The configuration and conformation of the 8α-methyl compounds are discussed with the aid of spectral data. The 8α-methyl group was found to eliminate essentially all the androgenic and anabolic activities in standard biological tests.

It has been well established that slight changes of the configuration of a biologically active molecule can vastly change its activity.[2] This characteristic has been studied in detail with steroids, where the effects upon biological activity of changing the configuration of substituents attached to carbon atoms on the periphery of the steroid nucleus are well documented.[3] However, the greatest changes in the overall shape of a steroid nucleus result from modification of the stereochemistry of the backbone of the molecule; of the backbone atoms, C-8 and C-9 cause the largest changes in molecular shape.

Several syntheses of 8-iso[4] and 9-iso steroids[5a] have been reported but less has been done with regard to the placement of a substituent at these centers.[5b] Continuing investigations of 8α-methyl steroid type antibiotics[6] have added interest in backbone substituted steroids. The preparation of an 8α-methyl steroid with other backbone carbon atoms possessing the natural configuration has been the basis of two studies.[7] The direct methylation of a 7-keto-9(11)-ene steroid has been reported to yield an 8α-methyl derivative;[8] the stereochemical assignment (first given as 8β)[9] is most likely correct but it is based upon tenuous spectroscopic interpretation. Recently an 8α-methylestrane derivative was prepared by hydrogenolysis of a bicyclobutane estrane precursor.[10] This synthetic route involved a nonstereospecific addition of dibromocarbene to a 6-ene, easily available only with ring-A aromatic steroids. The purpose of this present study was to develop a general, stereospecific synthesis of 8α-methyl steroids and then to evaluate such structural change upon hormonal activity.

The introduction of an 8α hydrogen or 8α substituent makes the B/C ring juncture cis, greatly changing the shape of the steroid nucleus. With the A/B and C/D ring junctures remaining trans, either ring B or ring C must be in a boat or twist conformation in these 8α steroids. In the C-boat or twist conformers, there is extreme steric hindrance because of the C-18 and C-19 angular methyl groups while the B-boat or twist conformers suffer only relatively minor hydrogen–angular methyl interactions. Thus, the B-boat or twist conformations would be preferred.



8α-methyl B boat

8α-methyl C boat

The B-boat conformers have a shape quite different from normal 8β steroids, but the distance between C-3 and C-17 remains approximately the same; for testosterone, 8-isotestosterone, and 8α-methyltestosterone, this distance on Dreiding models is virtually identical. If the C-3 to C-17 distance is important for biological activity, one would predict that 8α steroid hormones

(1) This work was supported, in part, by Grant No. CY-04284, National Cancer Institute, U. S. Public Health Service.

(2) For example, see A. Burger, "Medicinal Chemistry," 3rd ed, Wiley–Interscience, New York, N. Y., 1970.

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959; N. Applezweig, "Steroid Drugs," McGraw-Hill, New York, N. Y. 1962.

(4) W. G. Dauben and L. Ahramjian, *J. Amer. Chem. Soc.*, **78**, 633 (1956); C. Djerassi, H. Bendas, and A. Segaloff, *J. Org. Chem.*, **21**, 1056 (1956); C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6362, 6377 (1956); W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. I. Jones, *ibid.*, **80**, 661 (1958); G. C. Buzby, Jr., *et al.*, *J. Med. Chem.*, **9**, 338 (1966); K. Kuriyama, M. Moriyama, T. Iwata, and K. Tori, *Tetrahedron Lett.*, 1661 (1968); D. K. Banerjee, B. Sugavanam, and G. Nadamuni, *ibid.*, 2771 (1968); R. Bucourt, D. Hinaut, J. C. Gasc, and G. Nominé, *Bull. Soc. Chim. Fr.*, 1920 (1969); A. H. Emasry and O. Gisvold, *J. Pharm. Sci.*, **59**, 449 (1970); von C. Rufer, E. Schröder, and H. Gibian, *Justus Liebigs Ann. Chem.*, 211 (1967).

(5) (a) W. G. Dauben and G. J. Fonken, *J. Amer. Chem. Soc.*, **81**, 4060 (1959); J. Castells, E. R. H. Jones, G. D. Meakins, and R. W. J. Williams, *J. Chem. Soc.*, 1159 (1959); S. J. Halkes and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 889 (1965); H. Els, G. Englert, A. Fürst, P. Reusser, and A. J. Schocher, *Helv. Chim. Acta*, **52**, 1157 (1969). (b) J. W. ApSimon and R. R. King, *Can. J. Chem.*, **47**, 1989 (1969).

(6) The antibiotic activity of these compounds is described by W. O. Godtfredsen, W. von Daehne, L. Tybring, and S. Vangedal, *J. Med. Chem.*, **9**, 15 (1966).

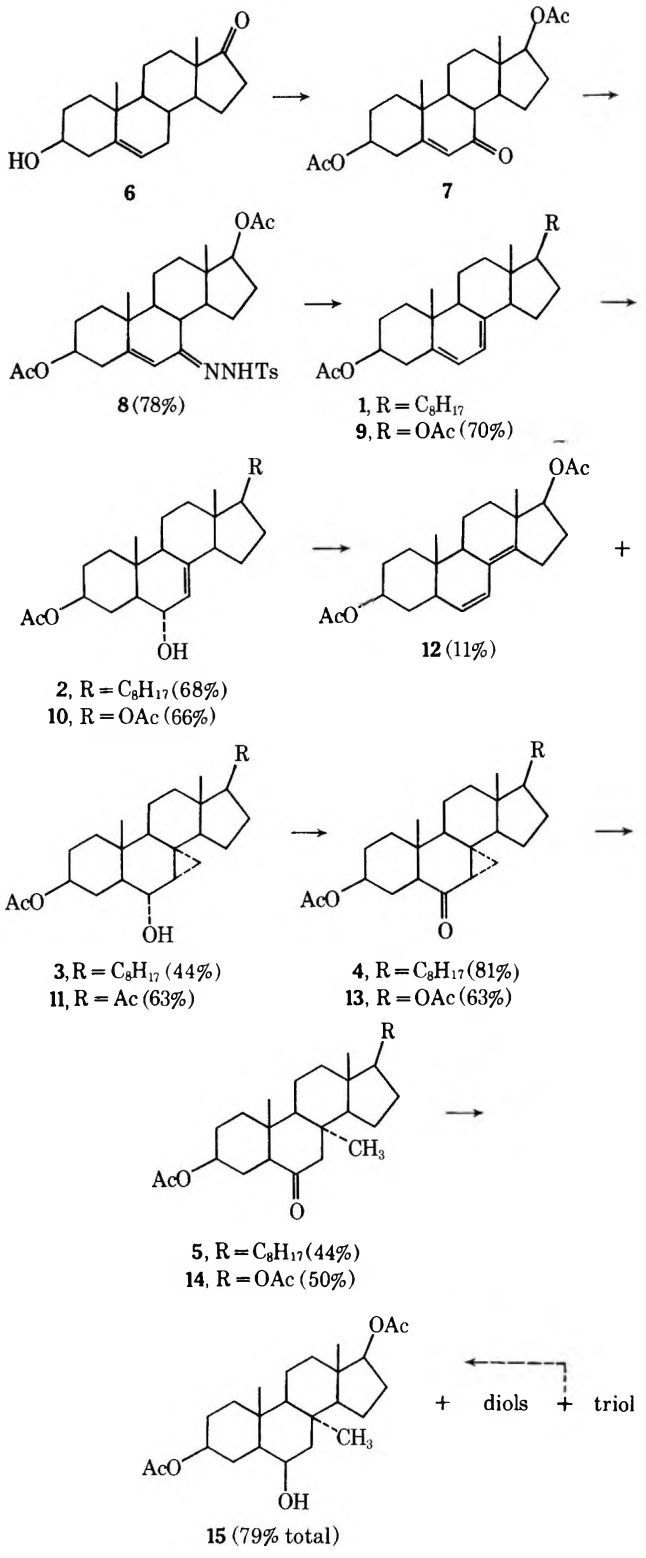
(7) W. Nagata and coworkers have stereoselectively made 8β-methyl steroids: W. Nagata, Proceedings of the Symposium on Drug Research, Montreal, Canada, June 1966; Japanese Patent 3166 (1967).

(8) G. Amiard, R. Heymés, T. V. Thuong, and J. Mathieu, *Bull. Soc. Chim. Fr.*, 2321 (1965).

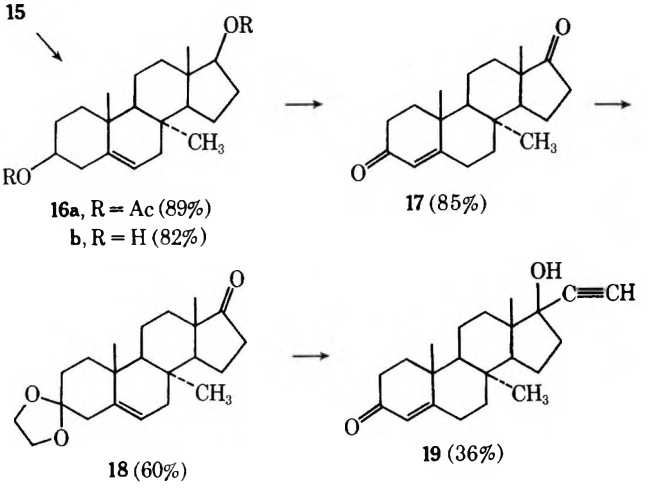
(9) G. Amiard, J. Mathieu, R. Heymés, and T. V. Thuong, *ibid.*, 1031 (1961).

(10) E. Galantay, N. Paolella, S. Barcza, R. V. Coombs, and H. P. Weber, *J. Amer. Chem. Soc.*, **92**, 5771 (1970).

SCHEME IA



SCHEME IB



would retain much of the androgenic and anabolic activities of their 8β isomers. Indeed, Djerassi found that 8-isotestosterone and 8-isoprogesterone have $^1/_3$ to $^1/_2$ the biological activity of the natural hormones.[11] Current receptor theory suggests that androgenic and anabolic receptors contact the β side of C-8 and that possibly the 8-iso steroids maintain significant biological activity by reacting at the receptors as the nearly planar intermediate between the C-boat and B-boat conformers.[11b] The introduction of the 8α-methyl group should affect this conformational situation and, in turn, the biological activity. However, it should be appreciated that drug–receptor interactions are not the only factors to be considered in studying androgenic and anabolic activities.[11c]

The general synthetic scheme followed was based upon previous findings in this laboratory and is shown in Scheme I. First, the methyl group was to be formed by a stereospecific reduction of the cyclopropyl ring of a 7α,8α-methano-6-one with lithium in liquid ammonia. In such a rigid ring system as that of a steroid, the cyclopropane bond that is better suited for the maximum π overlap in the transition state of the reduction[12] is clearly the one leading to the formation of an 8α-methyl group. The required cyclopropyl ketone was to be prepared from the related 6α alcohol, which in turn was to be obtained from the reaction of Simmons–Smith reagent (iodomethylzinc iodide) with the steroid 7-en-6α-ol. The stereospecific nature of the Simmons–Smith reaction with 2-cyclohexenols is well established,[13] the cyclopropane being formed on the same side of the molecule as the hydroxyl group. The desired steroid 7-en-6α-ol is known to be readily prepared by selective hydroboration of a 5,7 steroid diene.[14]

The portion of this synthetic route to cyclopropyl ketone **4** has been reported previously in the cholesterol series,[15] starting from the readily available steroid 5,7-diene **1**, but the experimental details were not given. In the present study, the reaction sequence was repeated and the yields obtained are given in Scheme I. The conversion of allylic alcohol **2** to cyclopropyl alcohol **3** was accompanied by a large production of a nonpolar side product which on the basis of detailed studies with the corresponding androstane compound **10** is certainly the product analogous to **12**. (Reaction

(11) (a) C. Djerassi, H. Bendas, and A. Segaloff, *J. Org. Chem.*, **21**, 1056 (1956); C. Djerassi, A. J. Manson, and H. Bendas, *Tetrahedron*, 22 (1957); (b) see J. A. Vida, "Androgens and Anabolic Agents," Academic Press, New York, N. Y., 1969. (c) A recent discussion with references is contained in a paper by M. E. Wolff and coworkers, *J. Med. Chem.*, **13**, 531 (1970).

(12) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966); T. Norin, *Acta Chem. Scand.*, **17**, 738 (1963).

(13) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **85**, 468 (1963).

(14) S. H. Burstein and H. J. Ringold, *ibid.*, **89**, 4722 (1967); H. Laurent, H. Muller, and R. Wiechert, *Chem. Ber.*, 3836 (1966); F. T. Bond and R. H. Cornelia, *Chem. Commun.*, 1189 (1968).

(15) F. T. Bond and R. H. Cornelia, *ibid.*, 1189 (1968). We gratefully thank the authors for a copy of the thesis of R. H. Cornelia, Oregon State University, 1968.

conditions were found during these studies which maximized the yield of **11** while minimizing dehydration to **12**.)

The cyclopropyl ketone **4** was reduced with lithium and ammonia, and the crude product reacetylated to yield 8α-methylcholestan-6-on-3β-ol acetate (**5**). The finding of a positive Cotton effect clearly corroborates the 8α-methyl stereochemistry since 8β-6-keto steroids are known to possess a large negative Cotton effect.[16]

17-Ethynyl-8α-methyltestosterone (**19**) was prepared from the readily available 5-androsten-17-one-3β-ol (**6**). A variety of synthetic routes have been reported for the conversion of a steroid 5-ene to a 5,7-diene,which is the essential intermediate in the synthetic scheme. In the present study, the conversion was achieved by a modified sequence. The corresponding 3β,17β-diacetate of **6** was converted to the 7-ketone derivative **7**, in 75% yield, by oxidation with solid chromium trioxide–pyridine complex in methylene chloride.[17] The ketone upon reaction with *p*-toluenesulfonylhydrazine in methanol without an acid catalyst gave the tosylhydrazone **8** in 78% yield. Treatment of this derivative with lithium hydride in refluxing toluene[18] yielded the 5,7-diene **9** in 70% yield. The overall yield of 40% compares favorably with yields obtained by the commonly employed *N*-bromosuccinimide process. However, the advantage of the present route is that the difficultly removed 4,6-diene is not a by-product.

The diene was hydroborated and the resulting alcohol **10** showed in the nmr the C-7 vinyl proton as the expected singlet, consistant with a dihedral angle of 90° with the C-6 β proton.[14] (Angular methyl groups appeared as expected at δ 0.87 and 0.67.) This alcohol was found to be extremely sensitive toward dehydration with Simmons–Smith reagent. The reaction had to be run while keeping the reaction bath temperature low (35–38°) and the amount of Simmons–Smith reagent carefully controlled. With these precautions, cyclopropyl alcohol **11** and diene **12** were obtained in yields of 63 and 11%, respectively. The diene **12** was the major product when more Simmons–Smith reagent was used, or when the bath temperature was higher.

Jones oxidation[19] of **11** gave cyclopropyl ketone **13**. The cyclopropyl ketone was reductively ring opened with lithium and ammonia, and the reaction product acetylated to give 8α-methylandrostan-6-one 3β,17β-diacetate (**14**). Since in the boat or twist conformation the angular methyl group C-18 is farthest away from the groupings at C-5 and C-6, the highest field resonance at δ 0.93 can be assigned to it. No definitive assignment can be given to the other two methyl group resonances since the exact conformation of ring B is not known. It is clear, however, that neither of the other two methyl nmr bands can be due to an 8β-methyl or the C-19 methyl group of an 8β steroid since either grouping would be expected to show a band at about δ 0.80. In agreement with this conclusion is the finding of a small positive Cotton effect in the CD of **14**. As mentioned earlier, this is unlike the large negative Cotton effect of 8β steroid 6-ones. Together, all these data indicate that the methylene bridge in cyclopropyl ketone **13** had to be α as predicted and assigned.

The reduction of the 6-ketone grouping in **14** with sodium borohydride was very slow, and as a result some hydrolysis (or reduction) of the acetate groups occurred. The reaction mixture was separated into a diacetoxy alcohol, two acetoxydiols, and a triol. It was found that these three materials could be selectively acetylated to yield **15**, indicating that the hydroxyl group at C-6 is sterically hindered. Thus, in a preparative run, the crude mixture could be directly reacetylated to give **15** in a total yield of 79%. No assignment of the 6-hydroxy stereochemistry can be made on the basis of spectral data or mechanistic predictions since the presence of an 8α-methyl group and the B twist conformations can give similar environments to both sides of the molecule around C-6.

Dehydration of the diacetoxy alcohol **15** with phosphorus oxychloride in pyridine gave the olefin **16** as the exclusive product (one vinyl proton multiplet at δ 5.35). The absence of any 6-ene product indicates that the hydroxyl in **15** possessed a β configuration since it is well established that dehydration of a 6β-ol in a 5α steroid under these conditions gives a 5-ene as the exclusive (or predominant) product.[20] Furthermore, equatorial (or pseudoequatorial) alcohols are known to dehydrate with difficulty,[21] while the dehydration of **15** was accomplished easily at 20°. The exclusive formation of the 5-ene may be also attributed to the fact that, when ring B is in a twist or boat conformation, no C-7 hydrogen atom can be trans coplanar with the leaving group. The assignment of a 6β-ol configuration to **15** permits assignments of its three nmr methyl resonances, *i.e.*, δ 0.92 to C-18 as discussed for **14**; the most deshielded methyl group must be C-19 (1.40 δ), leaving the 8α methyl to be at δ 1.08.

The diacetate olefin **16** was saponified and the resulting diol oxidized with Jones reagent.[19] The initial product was apparently a mixture of the Δ^4 and Δ^5 unsaturated ketones, but after alumina chromatography (activity III), only the pure Δ^4 isomer, 8α-methylandrost-4-ene-3,17-dione (**17**), was obtained. The ultraviolet spectrum of **17** [uv max 250 nm (ε 14,100)] reveals interesting information about the conformation. Since both 8β and 8-iso steroid Δ^4-3-ones display maxima at 242 nm,[4] the 8α-methyl group must introduce extra strain into ring A. A similar abnormal bathchromic shift has been reported for an 8α-methyl-1,4-dien-3-one and attributed to a slightly twisted boat conformation which developed to relieve steric interaction of the 8α-methyl group.[22] A similar conformation for **17** can be assumed.

For biological testing purposes, **17** was converted to 17-ethynyl-8α-methyltestosterone (**19**) *via* the monoketal **18**,[23] by reaction with solid lithium acetylide–EDTA,[24] and hydrolysis.

(16) P. Crabbé, "Optical Rotary Dispersion," Holden Day, San Francisco, Calif., 1965, pp 124–127.

(17) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).

(18) L. Cagliotti and P. Casselli, *Chim. Ind. (Milan)*, 559 (1963).

(19) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

(20) A. Schubert and C. Damker, *J. Prakt. Chem.*, **4**, 260 (1957); C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1786 (1952).

(21) The exception is when the carbon bearing the equatorial hydroxyl also bears a methyl group, in which case one of the methyl protons can line up for a trans coplanar *E2* elimination to give an exocyclic methylene. These topics are discussed in depth by D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, New York, N. Y., 1968, pp 101–111.

(22) See ref 8; *cf.* R. Bucourt, *Bull. Soc. Chim. Fr.*, 2081 (1964).

(23) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Amer. Chem. Soc.*, **76**, 1359 (1954).

(24) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).

Results of Biological Testing.—Using standard tests on **17** and **19**, it was found that the 8α-methyl group eliminates nearly all androgenic and anabolic activities found in the related 8β-H steroids. Only in the case of 8α-methylandrostenedione (**17**) was even slight androgenic activity maintained.

Experimental Section

Microanalyses and mass spectra were obtained from the Microchemical and Mass Spectrometry Laboratories, College of Chemistry, University of California. Optical rotations were taken in chloroform, nmr spectra in $CDCl_3$, and uv spectra in EtOH. Ir spectra were taken in chloroform and therefore may vary from expected CCl_4 values by 5–10 cm^{-1}. "Usual work-up" will be used to mean extraction of the crude reaction mixture with an appropriately large amount of ether and then washing the ether extract twice with 5% HCl, 5% $NaHCO_3$, saturated NaCl, and water. Each group of washings was individually back extracted with ether before further washing of the parent ether solution. The ether solution was dried over magnesium sulfate and rotary evaporated to give a crude product which was chromatographed and recrystallized. Unless otherwise specified, column chromatographies were with Woelm neutral alumina (activity III). Crystallizations were in a mixture of methylene chloride and methanol or (for alcohols) in methylene chloride and hexane.

7-Cholestene-3β,6α-diol 3β-Acetate (2).—A solution of 10 g (0.023 mol) of 5,7-cholestadien-3β-ol acetate (**1**) in 200 ml of tetrahydrofuran was cooled in an ice bath. To this rapidly stirred solution under nitrogen was added dropwise 14 ml (0.014 mol) of 1.0 *M* diborane in tetrahydrofuran solution (Alfa Inorganics, Inc.). The ice bath was removed, and the solution was allowed to stir for 1 hr. The rapidly stirred solution was cooled in an ice bath, and 10 ml of water was carefully added, followed by 10 ml of 3 *N* NaOH and 20 ml of 15% H_2O_2 solution. The ice bath was removed for 1 hr and replaced as 25 ml of 5% ferrous sulfate in 2% sulfuric acid was carefully added. The resulting solution was poured into 2.5 l. of ether. The ethereal extracts were carefully washed with acidic ferrous sulfate solution and worked up in the usual way to give 7.2 g (69%) of **2**: mp 141–144° (lit.[15] mp 143–144°); ir 3400, 1725, 1250 cm^{-1}; nmr δ 5.2 (s, 1, C-7 vinyl proton with singlet characteristic of a dihedral angle of 90° with the proton at C-6), 3.75 (m, 1, proton on C-6), 4,6 (m, 1, C-3 proton).

7α,8α-Methanocholestane-3β,6α-diol 3β-Acetate (3).—To 350 ml of anhydrous ether was added, with stirring, 7.5 g of methylene iodide and 14 g of zinc–copper couple (freshly prepared by the method of Friedrich[25]). After two tiny crystals of iodine were added, the solution was stirred for 30 min at reflux. At the end of that time, the bath temperature was reduced to 35–38°. A solution of 7.0 g (0.016 mol) of **2** and 12.5 g of methylene iodide in 1 l. of anhydrous ether was added over 30 min. The mixture was stirred at 35° for 17 hr; then further portions of 7.0 g of zinc–copper couple and 6.6 g of methylene iodide were added. The mixture was stored for an additional 8 hr, 25 ml of saturated ammonium chloride was slowly added, and the usual work-up (but omitting acid wash) was followed. Chromatography of the crude product on Woelm basic alumina (activity III) gave 3.0 g (44%) of **3**: mp 177–178° (lit.[15] mp 167–171°); ir 3400, 1725, 1230 cm^{-1}; nmr δ 3.70 (m, 1, proton on C-6), 0.2 (m, cyclopropyl protons). A major nonpolar side product was seen on tlc but not identified. On the basis of studies while making **11**, the material is certainly the diene corresponding to **12**.[26]

7α,8α-Methanocholestan-3β-ol-6-one Acetate (4).—To a solution of 1.5 g (3.0 mmol) of **3** in 600 ml of acetone at room temperature was added 1.8 ml of Jones reagent[19] with rapid stirring. The resulting solution was stirred for 10 min, and 5 ml of methanol was added dropwise to destroy excess Jones reagent. The usual work-up (but omitting the acid wash) was followed, including chromatography over basic alumina (activity III) to give 1.25 g (84%) of **4**: mp 167–169° (lit.[15] 165–168°); uv max 206 nm (ε 6000); ir 1685, 1725, 1250 cm^{-1}.

8α-Methylcholestan-3β-ol-6-one Acetate (5).—To 350 ml of dry[27] distilled liquid ammonia was added 0.2 g (0.028 mol) of lithium wire, and to the resulting blue solution which had been stirred for 20 min was added 1.0 g (0.014 mol) of anhydrous *tert*-butyl alcohol, followed by 1.25 g (3.0 mmol) of **4** and 1.0 g (0.014 mol) of anhydrous *tert*-butyl alcohol in 225 ml of anhydrous ether over 10 min. The resulting solution was stirred for 30 min under nitrogen and then 50 ml of saturated ammonium chloride solution was very carefully added dropwise, followed by 200 ml of glyme. The Dry Ice condenser and Dry Ice bath were removed and the ammonia was allowed to evaporate. The remaining glyme mixture was extracted with 3 l. of ether and worked up in the usual way. The crude product was dissolved in 25 ml of anhydrous pyridine containing 4 ml of acetic anhydride and the solution was heated on a steam bath for 1 hr. The usual work-up gave 550 mg (44%) of **5**: mp 150–151°; ORD (*c* 0.067, dioxane)[28] $[\Phi]_{317}$ +751°, $[\Phi]_{286}$ +217°; $[\alpha]^{26}D$ +17° (c 0.184); ir 1725, 1250, 1708 cm^{-1}; nmr δ 1.26 (new s, 3).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.57 H, 11.03.

5-Androstene-3β,17β-diol 7-Tosylhydrazone 3β,17β-Diacetate (8).—In 2 l. of methanol was dissolved 93 g (0.24 mol) of 5-androsten-7-one-3β,17β-diol diacetate (**7**)[17,29] and 100 g (0.54 mol) of *p*-toluenesulfonylhydrazine. The solution was refluxed for 5 hr under nitrogen and cooled, and the solvent was rotary evaporated at 30°. The resulting yellow oil was dissolved in 2 l. of methylene chloride and quickly washed through neutral alumina (activity III) with methylene chloride. The methylene chloride was rotary evaporated and the crude, oily product slowly crystallized to yield 105 g (78%) of **8** in three crops. (Rapid crystallization produced crystals contaminated with tosylhydrazine, which significantly lowers the yield of diene in the next step. The tosylhydrazine can be seen on tlc with phosphomolybdic acid, but is unstained by acidic ceric sulfate. Using less tosylhydrazine in the reaction gave much unreacted **8**.) The melting point of **8** is 201–203° dec; ir 3300 small peak, 1650 d, 1720, 1250 cm^{-1}; nmr δ 2.0 (s, 6, acetate), 4.7 (m, 2, C-3 and C-17 protons),[30] 7.2 and 7.7 (two d of d, 4, tosyl group aromatic protons), 6.1 (s, 1, vinyl).

Anal. Calcd for $C_{30}H_{40}O_6N_2S$: C, 64.51; H, 7.16. Found: C, 64.45; H, 7.18.

5,7-Androstadiene-3β,17β-diol 3β,17β-Diacetate (9).—A solution of 105 g (14.4 mol) of lithium hydride and 105 g (0.19 mol) of **8** in 4 l. of toluene was refluxed under nitrogen for 8 hr.[18] The solution was cooled and filtered through a sintered-glass funnel into a suction flask containing 200 ml 5% of sulfuric acid. The funnel was washed with toluene and anhydrous ether.[31] The toluene–ether solution was rotary evaporated to 2 l. and worked up in the usual way, chromatographed, and crystallized to yield 44.3 g (67%) of **9**.[32] The properties of **9** are mp 128–131° (lit.[33] mp 132°) and uv max 270, 280 nm (ε 10,500); no absorption at 230–240 nm was seen in the crude product or mother liquor of **9**, indicating no 4,6 diene product.

(25) L. Friedrich, Thesis, University of California, Berkeley, 1966; *cf.* R. E. Shank and H. Schechter, *J. Org. Chem.*, **24**, 1825 (1959). Friedrich's modification: "Into a 250-ml Erlenmeyer flask were placed 49.2 g of zinc dust and a large teflon magnetic stir bar. The zinc dust was washed with four 40-ml portions of 3% aqueous HCl. During each wash, the mixture was stirred vigorously for 1 min. The zinc was washed in the same manner with seven 100-ml portions of distilled water, and after the fifth wash the porous-looking zinc became a dense powder again. It was then washed with two 75-ml portions of 2% aqueous $CuSO_4$ $(H_2O)_4$ and six 100-ml portions of distilled water. After the fifth water wash, the material became a powder again. The zinc–copper couple was finally washed with four 100-ml portions of absolute ethanol and five 100-ml portions of anhydrous ether, and the last traces of ether were removed by a slow nitrogen stream passing over the couple's surface. The couple was stored over P_2O_5 under vacuum and used within 1 day of preparation."

(26) The procedure for making **11** was carefully developed so that the yield of cyclopropyl alcohol was high while keeping diene yield low. Thus, the procedure for **11** is recommended to be followed for making **3**.

(27) The ammonia must be dry to minimize reduction of the ketone.

(28) For comparison with **14**, this ORD corresponds to a CD of $[\theta]_{300} = +441$.

(29) H. J. Ringold, *J. Amer. Chem. Soc.*, **82**, 961 (1960).

(30) These absorptions appear for all the steroid acetates and will not be listed again.

(31) The large amount of recovered lithium hydride can be safely destroyed by suspending it in 1 l. of hexane and adding methanol, dropwise, over 3 days.

(32) Another 3.5 g of **9** was obtained by treating the dried mother liquor of **8** with lithium hydride in the same manner, bringing the total yield of diene **9** to 47.7 g or 40% from olefin **6**.

(33) R. Butenandt, *Ber.*, **71**, 1316 (1938).

7-Androstene-3β,6α,17β-triol 3β,17β-Diacetate (10).—In 4 l. of tetrahydrofuran was dissolved 45 g (0.12 mol) of diene **9** under nitrogen, and the mixture was cooled in an ice bath. To this rapidly stirred solution was added dropwise 100 ml (0.1 mol) of 1.0 *M* diborane in THF solution. The ice bath was removed, and the solution was allowed to stir for 1.5 hr. The rapidly stirred solution was cooled in an ice bath, and 50 ml of water was carefully added dropwise, followed by 9 ml of 5% NaOH solution. The 5% base solution was thereafter added dropwise until the pH of the reaction mixture reached just 9–10 as indicated on moist wide-range pH paper. (Excess base reduces the yield of **10** through saponification.) To the alkaline solution was added 60 ml of 15% hydrogen peroxide, and the pH of the mixture was checked again and adjusted if necessary. The ice bath was removed and the solution stirred under nitrogen for 1 hr. Acidic ferrous sulfate was added dropwise to the cooled mixture and work-up proceeded as with **2**. The yield after chromatography was 31 g (76% based on recovered diene) of **10** as amorphous dried flakes (one spot, tlc) and 5.6 g of recovered diene **9**. Product **10** resisted all attempts at crystallization, even after preparative tlc. The spectral properties of **10** are ir 3400, 1720, 1250 cm^{-1}; nmr δ 5.15 (s, 1, C-7 vinyl proton with singlet characteristic of a dihedral angle of 90° with the proton at C-6),[14] 3.75 (*m*, 1, proton on C-6), 0.87 (*s*, 3, C-19 methyl), 0.67 (s, 3, C-18 methyl).

Anal. Calcd $C_{23}H_{34}O_5$: *m/e* 290.2406. Found: *m/e* 290.2406.

7α,8α-Methanoandrostane-3β,6β,17β-triol 3β,17β-Diacetate (11).—The following is the procedure found to maximize the yield of **11** while keeping the yield of diene **12** minimized. To 1.5 l. of anhydrous ether was added 8 g of fresh zinc–copper couple,[25] 33 g of methylene iodide, and three tiny crystals of iodine. The mixture was refluxed for 45 min and then 14.1 g (0.048 mol) of **10** in 150 ml of anhydrous ether was added in one portion. The bath under the reaction was maintained at 35–38° for 24 hr, causing a very slow rate of reflux. At the end of this reflux period, a solution prepared by refluxing 33 g of methylene iodide, 8 g of zinc-copper couple, and three tiny crystals of iodine in 100 ml anhydrous ether for 45 min was added to the reaction mixture. The bath was maintained at 35–38° for an additional 24 hr, and 15 ml of saturated aqueous ammonium chloride was added to the cooled solution. Usual work-up (but omitting acid wash), chromatography on basic alumina (activity III), and crystallization gave 9.1 g (63%) of **11** and 1.4 g (11%) of diene **12**. The properties of **11** are mp 221–222°; $[\alpha]^{26}D$ +43° (*c* 0.105); ir 3400, 1725 cm^{-1}; nmr δ 0.3 (broad m, 3).

Anal. Calcd for $C_{24}H_{36}O_5$ (**11**): C, 71.26; H, 8.79. Found: C, 71.19; H, 8.95.

The properties of diene **12** are mp 150–151°; $[\alpha]^{26}D$ +162° (*c* 0.10); uv max 248 nm (ε 23,500); ir 1725 cm^{-1}; nmr δ 6.1 (d of d, 1, J = 3, 9 Hz), 5.3 (d of d, 1, J = 3, 9 Hz), 0.85 (s, 6, angular methyls).

Anal. Calcd for $C_{23}H_{32}O_4$ (**12**): C, 74.16; H, 8.66. Found: C, 74.07; H, 8.75.

7α,8α-Methanoandrostane-3β,17β-diol-6-one 3β,17β-Diacetate (13).—In 1 l. of acetone was dissolved 9.5 g (24 mmol) of **11** and the mixture was cooled in an ice bath. To the cooled solution was added dropwise 10.0 ml of Jones reagent.[19] The ice bath was removed, the mixture was stirred for 10 min, 5 ml of methanol was added, and reaction mixture was stirred for an additional 2 min. The reaction was worked up in the usual way (but with no acid wash) and chromatographed over basic alumina (activity III) to yield 6.2 g (63%) of **13**: mp 174–175°; $[\alpha]^{26}D$ 0° (*c* 0.129); uv max 205 nm (ε 6100); ir 1725, 1685, 1250 cm^{-1}; nmr δ 0.83 (s, 6, angular methyl groups).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.61; H, 8.46.

8α-Methylandrostane-3β,17β-diol-6-one 3β,17β-Diacetate (14).—Following the procedure for **5**, 3.5 l. of anhydrous ammonia was distilled and to it was added 1.5 g (0.21 g-atom) of lithium wire. The lithium in ammonia solution was stirred for 20 min and 5.0 g (0.067 mol) of anhydrous *tert*-butyl alcohol was added, followed by a solution of 5.0 g (0.012 mol) of **13** and 10.0 g (0.135 mol) of anhydrous *tert*-butyl alcohol in 200 ml of anhydrous ether and 15 ml of anhydrous hexane. The solution of **13** was added over 10 min, the resulting mixture was stirred for 30 min, and 50 ml of saturated aqueous ammonium chloride solution was very carefully added dropwise, followed by 200 ml of glyme. The Dry Ice condenser and Dry Ice bath were removed, and the ammonia was allowed to evaporate. The remaining glyme mixture was processed in the usual fashion, and the crude product was acetylated as in the procedure for **5** and column chromatographed to give 2.5 g (50%) of **14**: mp 224–225°; $[\alpha]^{26}D$ +9° (*c* 0.129); CD (*c* 0.089, dioxane) $[\theta]_{298}$ +50; ir 1708, 1725, 1250 cm^{-1}; nmr δ 1.21 (s, 3), 1.06 (s, 3), 0.93 (s, 3).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 70.97; H, 8.88.

8α-Methylandrostane-3β,6β,17β-triol 3β,17β-Diacetate (15).—To a solution of 1.4 g (3.5 mmol) of **14** in 3.5 l. of distilled ethanol under a nitrogen atmosphere and at room temperature there was added 75 mg (2.0 mmol) of sodium borohydride. The solution was stirred for 6 hr, an additional 70 mg (2.0 mmol) of sodium borohydride was added, and 14 hr later, another 65 mg (1.7 mmol) was added. Less stirring time left unreacted ketone. After 3 hr of additional stirring, 50 ml of 5% HCl was added, and the resulting ethanol solution was rotary evaporated at 35° to 200 ml. The resulting solution was worked up in the usual way and the crude product was chromatographed over neutral alumina (activity IV) to give 750 mg (52%) of **15**. In addition, 210 and 96 mg of two diol monoacetates were collected, as well as 180 mg of a triol. These side products were individually dissolved in 20 ml anhydrous pyridine and acetylated with 1 ml of acetic anhydride by stirring at room temperature under nitrogen for 5 hr. Individual work-up of each and chromatography over neutral alumina (activity IV) gave **15** in each case, 350-mg total, bringing the combined yield of **15** to 1.1 g (79%). The properties of **15** are mp 169–170°; $[\alpha]^{26}D$ −54° (*c* 0.090); ir 3400, 1725, 1250 cm^{-1}; nmr δ 1.40 (s, 3), 1.08 (s, 3), 0.92 (s, 3), 4.0 (m, 1).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.12; H, 9.65.

8α-Methyl-5-androstene-3β,17β-diol 3β,17β-Diacetate (16).—To an ice-bath cooled solution of 1.2 g (3.0 mmol) of **15** in 34 ml of pyridine was added 9.6 ml (26 g, 0.017 mol) of phosphorus oxychloride. The ice bath was removed and the mixture was allowed to stir under nitrogen at 20° overnight. Water was very carefully added dropwise to the mixture, and the reaction was worked up in the usual manner to give 1.023 g (89%) of **16**: mp 181–182°; $[\alpha]^{26}D$ 0° (*c* 0.149); ir 1725, 1250 cm^{-1}; nmr δ 5.32 (m, 1), 1.22 (s, 3), 1.00 (s, 3), 0.89 (s, 3).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.93; H, 9.25.

8α-Methyl-4-androstene-3,17-dione (17).—To 900 mg (2.3 mmol) of **16** in 2.3 l. of methanol was added 1.0 g (17 mmol) of potassium hydroxide in 50 ml of methanol containing 2 ml of water. The resulting mixture was refluxed under nitrogen for 3.25 hr, after which 25 ml of saturated sodium chloride was added, and the methanol solution was rotary evaporated at 35° to 200 ml. Usual work-up, with last traces of water in the crude product removed by rotary evaporation of a benzene azeotrope, gave 580 mg (82%) of crude diol **15b**, mp 156–173°. The diol was oxidized with 60 ml of chromium trioxide–pyridine complex methylene chloride solution (6.0 g of chromium trioxide, 9.49 g of pyridine, in 150 ml of methylene chloride).[34] Usual work-up gave 520 mg of crude product which showed two major products on tlc. Chromatography and crystallization gave 410 mg (85%) of **17**: mp 164–165°; $[\alpha]^{26}D$ +220° (*c* 0.083); uv max 250 nm (ε 14,100); ir 1730, 1655 cm^{-1}; nmr δ 6.0 (s, 1), 1.35 (s, 3), 1.11 (s, 3), 1.08 (s, 3).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.77; H, 9.46.

8α-Methyl-4-androstene-3,17-dione 3-Ethylene Ketal (18).—A solution of 100 ml of 2-methyl-2-ethyl-1,3-dioxolane[23] in 500 ml of *n*-hexane was passed through 250 g of basic alumina (activity III). By this procedure, less than 0.5% ethylene glycol remained in the ketal after the hexane was rotary evaporated. In 30 ml of ketal was dissolved 250 mg (0.83 mmol) of **17** along with 8 mg of *p*-toluenesulfonic acid monohydrate. The mixture was very slowly distilled under dry nitrogen over 5.5 hr so that only 5 ml remained; 50 ml of reagent benzene was added and the mixture was extracted with 100 ml of dry ether. The ether–benzene solution was washed with 5% sodium bicarbonate and with water, and organic solvents were rotary evaporated. The residue, 310 mg of brown oil, was chromatographed over basic alumina (activity III) to give 128 mg of monoketal **18**, no diketal, and 96 mg of recovered starting material. The 96 mg of recovered starting material and 60 mg more of **17** was treated the same way to give an additional 105 mg of monoketal **18**.

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

Thus, from 310 mg of **17**, 233 mg (66%) of **18** was obtained. The properties of **18** are mp 173–174°; ir 1730 cm^{-1}; nmr 5.3 (s, 1, vinyl), 4.0 (m, 4, ethylene), 1.05 (s, 3), 1.13 (s, 3), 1.20 (s, 3).

Anal. Calcd for $C_{22}H_{32}O_3$: *m/e* 344.2351. Found: *m/e* 344.2349.

17-Ethynyl-8α-methyltestosterone (19).—In 170 ml of spectroquality dioxane under nitrogen in a 500-ml three-neck flask was bubbled acetylene which had been passed through three sulfuric acid wash bottles, one empty trap, one KOH cylinder, and one calcium chloride trap. After 5 min of bubbling, 5.0 g (0.055 mol) of lithium acetylide–EDTA complex[24] (Foote Mineral Co.) was added. The mixture was stirred for 10 min while acetylene bubbling was continued, and then 185 mg (0.54 mmol) of **18** in 120 ml of dioxane was added dropwise over 25 min. Acetylene bubbling was continued for an additional 40 min. The resulting mixture, under nitrogen, was stirred overnight at room temperature (total 22.5 hr), 5 ml of saturated aqueous ammonium chloride solution was carefully added with a micropipette, and 100 ml of a 1:1 mixture of water and concentrated HCl was added. The resulting solution was heated on a steam bath 1.25 hr and cooled and usual work-up gave 205 mg of a yellow oil. The material was purified by preliminary chromatography on neutral alumina (activity IV) and the resulting 120 mg of a yellow semisolid was separated by preparative thin layer chromatography to give 63 mg (36%) of **19** and 20 mg of yellow oil containing **17**. The properties of **19** are mp 230–231°; $[\alpha]^{26}D$ +88° (*c* 0.025); uv max 250 nm (ε 14,100); ir 3350, 1660 cm^{-1}; nmr δ 6.0 (s, 1), 1.33 (s, 3), 1.10 (s, 3), 1.07 (s, 3).

Anal. Calcd for $C_{22}H_{30}O_2$: *m/e* 326.2247. Found: *m/e* 326.2252.

Registry No.—**2**, 17181-88-3; **3**, 31327-29-4; **4**, 31327-30-7; **5**, 31327-31-8; **8**, 31327-32-9; **9**, 31327-33-0; **10**, 31327-34-1; **11**, 31337-76-5; **12**, 31337-75-4; **13**, 31327-35-2; **14**, 31327-36-3; **15**, 31428-83-8; **16a**, 31385-44-1; **17**, 31337-34-5; **18**, 31337-35-6; **19**, 31337-36-7.

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The Stereochemistry of Vinyl Phosphates from the Perkow Reaction and the Phosphorylation of Enolates[1]

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The predominant stereochemistry of vinyl phosphates resultant from the reactions of α-halo ketones with trialkyl phosphites involves the *E* configuration, *i.e.*, $(RO)_2P(=O)O_A{>}C{=}C{<}^{H_B}_{Y}$ for A = Ph, H_A; Y = Ph, alkyl, Cl, Br. The assignment of stereochemistry is based on a combination of nmr spectral effects including (a) the differentiation of cis and trans 1,2-vinyl protons by their J_{HH} coupling constants, (b) a downfield shift for H_B when cis to phosphate and A = Ph in the presence of boron trifluoride etherate, and (c) the application of Tobey–Pascual substituent shielding constants. The phosphorylation of several potassium or lithium enolates with diethyl phosphorochloridate gives predominantly vinyl phosphates. In two cases these also have the *E* configuration. Several vinyl phosphates are found to have $J_{allyl_{POCCH}}$ coupling constants, trans > cis. Deuteriobenzene solvent induced shifts are briefly discussed.

The reactions of α-halo ketones with trialkyl phosphites lead to either ketophosphonates or, more usually, to vinyl phosphates (Perkow reaction).[3] The stereoisomerism of these vinyl phosphates has been previously discussed,[4] although rigorous assignment of structure has often been lacking. In one case, an unambiguous assignment[4c] was unfortunately inverted by error.[3a] We now report that the stereochemistry of vinyl phosphates can be determined, in a number of cases, by a combination of nmr techniques including the assignment of cis and trans groups on an ethylene by the method of Tobey[5a] and Pascual.[5b] We have also phosphorylated several enolates to give mainly vinyl phosphates whose stereochemistry can be correlated with those obtained from the Perkow reaction. Although some enolates have previously been phosphorylated on oxygen,[3a] the resultant vinyl phosphates have not previously been correlated with those arising from the Perkow reaction.[5c]

Results and Discussion

Phosphorylation of Enolates.—A number of potassium or lithium enolates were prepared under kinetic control conditions by the reaction of potassium or lithium triphenylmethide with the respective ketone (Scheme I).[6] Reaction of these enolates with diethyl phosphorochloridate gives the vinyl phosphate as the exclusive product (Table I) except in the case of acetophenone where some ketophosphonate (11%) is also formed. Equilibrium control formation of several enolates[6b] gave the same results.

Our phosphorylation results parallel the reactions of enolates with acetyl chloride or chlorotrimethylsilane in that bond formation occurs on oxygen in most cases.[6,7] The small yield of **16** could arise from either direct C-phosphorylation of the enolate or from the

(1) This investigation was supported by Grant No. AF-AFOSR 1170-66, 1170-67 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research, and by the National Science Foundation. This is part XV of the series, Organophosphorus Chemistry.

(2) To whom correspondence should be addressed.

(3) (a) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); (b) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965); (c) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

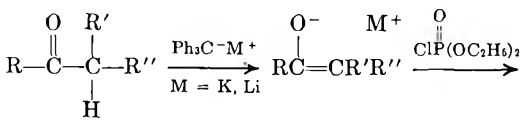
(4) (a) J. C. Craig, M. D. Bergenthal, I. Fleming, and J. Harley-Mason, *Angew. Chem., Int. Ed. Engl.*, **8**, 429 (1969); (b) J. C. Craig and M. Moyle, *J. Chem. Soc.*, 3712 (1963); (c) A. R. Stiles, C. A. Reilly, G. R. Pollard, C. H. Tieman, L. F. Ward, D. D. Philips, S. B. Soloway, and R. R. Whetstone, *J. Org. Chem.*, **26**, 3960 (1961).

(5) (a) S. W. Tobey, *ibid.*, **34**, 1281 (1969); (b) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966); (c) for recent work on the stereochemistry of the thiophosphorylation of enolates, see B. Miller, H. Margulies, T. Drabb, Jr., and R. Wayne, *Tetrahedron Lett.*, 3801, 3805 (1970).

(6) (a) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 272–275; (b) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

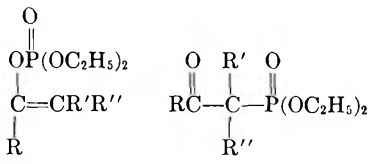
(7) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462 (1968).

SCHEME I



1, R = Ph; R′ = R″ = H
2, R = Ph; R′ = CH_3; R″ = H
3, R = Ph; R′ = R″ = CH_3
4, R = Ph; R′ = Ph; R″ = H
5, R, R′ = $-(CH_2)_4-$; R″ = H

6
7
8
9
10



11
12a,b
13
14a,b
15

16, R′ = R″ H
17, R′ = CH_3; R″ = H

TABLE I

PHOSPHORYLATION OF ENOLATES WITH DIETHYL PHOSPHOROCHLORIDATE

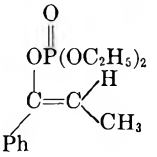
Ketone	Procedure[a]	Yields, %[b] Keto-phosphonate	Vinyl phosphate
Acetophenone	A	16, 11	11, 61
Propiophenone	B,C		12, 75,[c] 47[d]
Isobutyrophenone	A		13, 58
Benzyl phenyl ketone	B,C		14, 41,[c] 47[d]
Cyclohexanone	A		15, 62

[a] See Experimental Section for reaction conditions. [b] Determined by vpc or nmr methods (see Experimental Section). [c] Kinetic control conditions. [d] Equilibrium control conditions.

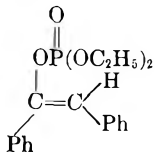
reaction of excess enolate with the O-phosphorylated product. The latter pathway is involved in the C-acylation of enolates.[6a] Evidence for direct C-phosphorylation was found as follows. Treatment of the potassium enolate of acetophenone (**6**) with diethyl phenylvinyl phosphate (**11**) or diethyl cyclohexenyl phosphate (**15**) does not lead to any C-phosphorylation or other discernable reaction.[8]

The demonstration of O-phosphorylation of enolates serves as further evidence against the involvement of enolate halophosphonium ion pairs in the Perkow reaction.[3b,c] If α-halo ketones reacted with trialkyl phosphites *via* attack on halogen, the resultant ion pairs should then interact to give O-phosphorylation. The Perkow reaction, however, results in ketophosphonate formation from α-bromoacetophenone and α-bromopropiophenone, in major and minor yields, respectively.[9]

The formation of vinyl phosphates **12** and **14** by the O-phosphorylation of enolates under kinetic or equilibrium control conditions leads to only one of the two possible isomers in each case. These isomers have now been shown to have the *E* configurations[10] **12a** and **14a**. While we do not have direct evidence,[11] **14a** may be more stable than the *trans*-stilbene **14b**.



12a



14a

Thus both (*E*)-1-(4-morpholino)-1,2-diphenylethylene[12] and (*E*)-1-toluenesulfonyl-1,2-diphenylethylene[13] (both *cis*-stilbene derivatives) are more stable than the corresponding *trans*-stilbene isomers.

Our finding of stereospecific phosphorylation under both kinetic and equilibrium control conditions is in contrast to the acetylation[14] and trimethylsilylation[6b] of potassium enolates in glyme wherein opposing ratios of isomeric products are formed under the two sets of conditions. Although the 1,2-diphenylethylene system may be a special case, the 1-phenyl-2-methylethylene system should be more typical and comparable to known cases.[6b] The effects of solvent, cation, substrate, and other factors on the stereochemistry of the phosphorylation of enolates need to be further investigated.[5c]

Stereochemistry of the Perkow Reaction.—Table II indicates nmr data obtained on vinyl phosphates formed in the reactions of α-halo ketones, α,α-dihalo ketones, and α-haloaldehydes with triethyl phosphite (TEP) or trimethyl phosphite (TMP). In many of the cases, one isomeric vinyl phosphate predominates or is the sole product. This isomer is identical (for **12** and **14**) with the one formed in the phosphorylation of the corresponding enolate.

Our initial attempts at determining the stereochemistry of the predominant isomer **14a** by the nuclear Overhauser effect[15] or by reductive conversion to the corresponding stilbene[16] failed. Thus reaction of the dimethyl 1,2-diphenylvinyl phosphate mixture **14c,d** with lithium and ammonia under various conditions gave *trans*-stilbene as the sole product; *i.e.*, equilibration to the more stable *trans*-stilbenyl carbanion occurs under the reaction conditions.[17] While this method might work for other cases, especially those that have been used in the Board olefin synthesis,[18] we needed other methods for phenyl-substituted olefins.

Several attempts at the unambiguous synthesis of a vinyl phosphate of known stereochemistry also failed. Thus we could not phosphorylate the erythro bromohydrin **19** derived from *trans*-stilbene epoxide (**18a**,

(8) House, *et al.*, have similarly shown that silyl ethers do not undergo trans silylation with enolate anions.[6b]

(9) Data and a summary of arguments relevant to the mechanism of the Perkow reaction have been presented.[3c]

(10) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

(11) (a) Attempted isomerization of **14a,b** or **14a** with iodine in various solvents gave no change or led to the destruction of the vinyl phosphate(s). We had previously argued that the enolate of phenyl benzyl ketone should be more stable as a *trans*-stilbene derivative.[11b] It now appears that both kinetic and equilibrium control conditions lead to a phosphorylated *cis*-stilbene derivative. (b) I. J. Borowitz, P. E. Rusek, and R. Virkhaus, *J. Org. Chem.*, **34**, 1595 (1969).

(12) M. E. Munk and Y. K. Kim, *ibid.*, **30**, 3705 (1965).

(13) S. J. Cristol and P. Pappas, *ibid.*, **28**, 2066 (1963).

(14) H. O. House and V. Kramer, *ibid.*, **28**, 3362 (1963).

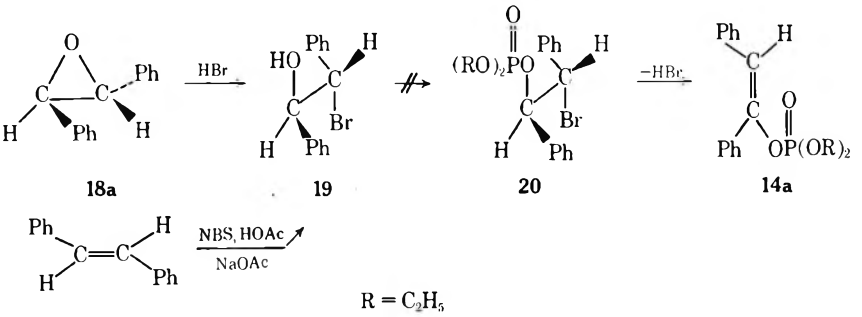
(15) Performed by Mr. Hara of JEOLCO on JEOLCO 60- and 100-MHz nmr spectrometers.

(16) Alicyclic vinyl phosphates have thus been reduced to olefins: (a) M. Fetizon, M. Jurison, and N. T. Anh, *Chem. Commun.*, 112 (1969); (b) R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, 2145 (1969).

(17) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 130–135.

(18) M. C. Hoff, K. W. Greenlee, and C. E. Boord, *J. Amer. Chem. Soc.*, **73**, 3329 (1951).

SCHEME II



18a 19 20 14a

(Scheme II). Attempts to directly convert **18a** to the corresponding phosphorylated chlorohydrin also failed. It had been hoped to then convert **20** to **14a** by a trans elimination.[19]

The successful approach to the stereochemical problem involved noting the changes in the nmr chemical shift for the vinyl proton β to the phosphate upon changing the solvent from diethyl ether to boron trifluoride etherate in diethyl ether. Ordinarily, a phosphate group behaves as an electron-donating group and it shields trans β-vinyl protons more than cis β-vinyl protons (see below for an estimate of this effect). Greater shielding (or deshielding) of trans vicinal vinyl protons as opposed to cis vicinal vinyl protons is found for a number of groups.[5a,b] A Lewis acid, such as boron trifluoride, should cause an increase of the net positive charge on phosphorus (of a vinyl phosphate) because of coordination with the PO "double bond." Such coordination compounds are well known.[20] The effect of this coordination should be a deshielding one for both cis and trans β-vinyl protons since the phosphate group will now be less electron donating. Whether the resultant change will be felt more by cis or trans β-vinyl protons is open to argument. Our results (Table II) indicate that the observed effect depends mainly upon the vicinal shielding (or deshielding) properties of the group geminal to phosphate. When this group is phenyl, the overall effect of boron trifluoride coordination of PO is a greater deshielding of the cis β-vinyl proton as opposed to the trans β-vinyl proton. That this overall effect may be due to the phenyl group, which shields trans and deshields cis β-vinyl protons,[5a,b] can be seen by comparing the results for **12a,b**, **14a,b**, **14c,d**, **38**, and **39** with those for the *gem*-methyl compounds **40**–**42**. In the latter set, boron trifluoride causes a relatively greater deshielding of the trans β-vinyl proton. Since many of the vinyl phosphates of interest to us had either *gem*-phenyl groups or were of otherwise determinable stereochemistry, the deshielding of cis β-vinyl protons by boron trifluoride for many cases could be used without ambiguity. In support of the proposal that boron trifluoride is coordinating with the oxygen of PO, we note a general deshielding of the methylene group of OC_2H_5 in all of the diethyl phosphates studied. Some of the data is included in Table II.

It had been anticipated that a cis β-vinyl proton would show little change for $\Delta = \delta_{CCl_4} - \delta_{C_6D_6}$ (other than a general effect experienced by all groups including TMS) since it is close to the bulky phosphate group. Furthermore benzene molecules were expected to orient themselves so as to be away from the negative (oxygen) end of the PO dipole. A trans β-vinyl proton was expected to show an upfield shift due to increased shielding by benzene molecules forming a "collision complex" at this "far end" of the molecule.[21]

The anticipated preferential shielding of a trans β-vinyl proton was found for **14**, **40**, and the related phosphorylated species **41** and **42**. The *gem*-phenyl phosphates **11** (and related species **38**, **39**), **12**, **31**, and **32**, however, exhibit a deshielding of the trans β-vinyl proton and a shielding of the cis β-vinyl proton. Our data indicate that factors additional to steric ones have to be considered. These may include the relative orientation of the phosphate group in various vinyl phosphates, an attraction of benzene molecules to the positive phosphorus, and a repulsion from the negative oxygen of the PO group. As evidence for the orientation of benzene molecules away from the oxygen end of PO, we cite the relatively greater shielding of methyl (+0.25 ppm) than methylene (+0.12 ppm) in the ethoxy group of **11**. Similar benzene solvent effects have been noted with esters[21c] and ketones.[21d]

The magnitude of our nmr effects was established for several cases of known stereochemistry (Table II). The deshielding of the cis β-vinyl proton in **15**, **22**, and **24** by BF_3 coordination with PO was found to be −0.145, −0.26, and −0.32 ppm, respectively. The geminal proton values for **22** and **24** were less affected (+0.03 and −0.06 ppm). The $\Delta = \delta_{CCl_4} - \delta_{C_6D_6}$ shifts were negative for **15**, **22**, and **24** (−0.24, −0.06, and −0.01 ppm). The reactions of α-bromoacetaldehyde (**21**) or α-chlorobutyraldehyde (**23**) with TMP gave the trans *E*-vinyl phosphates **22** and **24**, respectively, as established by the J_{HH} vinyl proton coupling constants of 12 and 12.6 Hz.[22]

Assuming that the above nmr effects hold for other vinyl phosphates, we conclude that α-chlorobenzyl phenyl ketone (**25**) reacts with TEP to give a 65:35 ratio of the *E*:*Z* isomers **14a** and **14b**. Similarly TMP gives **14c** and **14d**, with **14c** predominating. Phosphorylation

(19) Such an approach has been widely used to synthesize ethylenes of known stereochemistry.[12,13]

(20) (a) A. B. Burg and W. E. McKee, *J. Amer. Chem. Soc.*, **73**, 4590 (1951); (b) A. V. Topchiev, S. V. Z. Zangorodnii, and Y. M. Paushkin, "Boron Trifluoride and Its Compounds as Catalysts in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp 82–84.

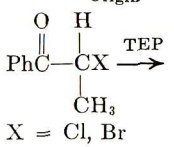
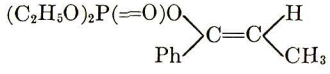
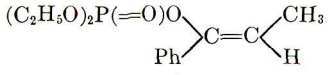
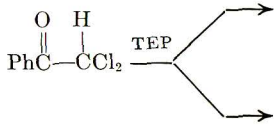
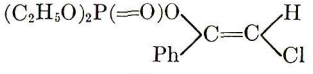
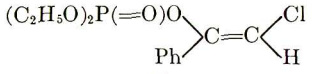
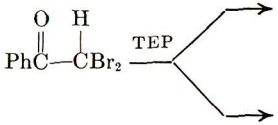
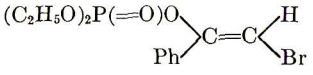
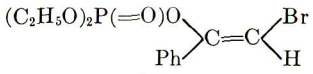
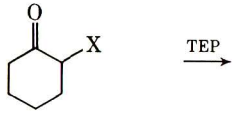
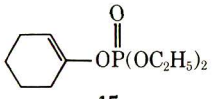
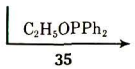
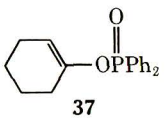
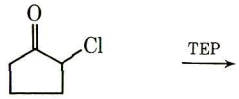
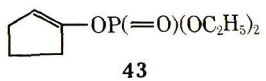
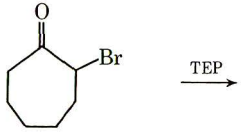
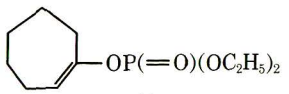
(21) Benzene solvent shifts for vinyl halides, acids, and esters have been found to be largest for trans β-vinyl protons: (a) F. Hruska, D. W. McBride, and T. Schaefer, *Can. J. Chem.*, **45**, 1081 (1967); (b) J. Ronague and D. H. Williams, *J. Chem. Soc.*, 2642 (1967); (c) A. Kemula and R. T. Iwamoto, *J. Phys. Chem.*, **72**, 2764 (1968); (d) M. Fétizon, J. Goré, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

(22) Cis 1,2-divinyl proton coupling constants of vinyl phosphates are 4.1–5.8 Hz and trans constants are 11.1–13.2 Hz. See J. P. Ferris, G. Goldstein, and D. J. Beaulieu, *J. Amer. Chem. Soc.*, **92**, 6598 (1970), and references therein.

TABLE II
VINYL PHOSPHATE SPECTRAL DATA

Origin	Compd	Isomer ratio	β-Vinyl H nmr: $-\delta_{Et_2O}$	$\Delta = \delta_{Et_2O} - \delta_{BF_3\text{-}Et_2O}$	$-\delta_{CCl_4}$	$\Delta = \delta_{CCl_4} - \delta_{C_6D_6}$	J_{POCCH}, Hz	Other data
25 → TEP	**14a** (*E*)	65[a]	6.42	−0.28	6.33	−0.15	1.0	Uv λ_{max}^{EtOH} 221 nm (4.16), 283.5 (4.25)
25 → TEP	**14b** (*Z*)	35[a]	6.79	−0.02	6.69	+0.30	2.5	Ir (CCl_4) 1605, 1645 cm^{-1}
25 → TMP	**14c** (*E*)	65	6.42	−0.25	6.34	−0.05	1.0	^{31}P nmr +4.0 ppm
	14d (*Z*)	35	6.75	−0.04	6.67	+0.28		
26 + TEP or 9 + $ClPO(OC_2H_5)_2$ →	**14a**		6.40	−0.26	6.32	−0.05		Uv λ_{max}^{EtOH} 221 nm (4.09), 283.5 (4.31)
25 or 26 →	$Ph_2P(=O)O$, Ph, H, Ph		6.22	−0.19	6.19	−0.05	*Ca.* 1.0	Uv λ_{max}^{EtOH} 274 nm (4.29), 283 (4.28); ^{31}P nmr −27.5 ppm
	36							
PhCCH$_2$Cl →	$(C_2H_5O)_2P(=O)O$, Ph, H_B, H_C			−0.28		+0.02		
			5.24		5.21		2.3 (Et_2O), 2.1 (CCl_4)	
	11			−0.01		−0.29		
		OCH_2				+0.12		
		CH_3				+0.25		
	$Ph_2P(=O)O$, Ph, H_B, H_C	H_B	5.05	−0.29	5.04	+0.07[b]	1.0	
		H_C	5.28	−0.06	5.21	−0.36	2.0	
	38							
	$PhP(=O)O(C_4H_9O)$, Ph, H_B, H_C	H_B	5.18	−0.21	5.12	+0.02[b]	1.5	
		H_C	5.20	0.00	5.20	−0.30	2.5	
		OCH_2		−0.30		0.00		
		CH_3				+0.20		
	39							
CH$_3$CCH$_2$Cl →	$(C_2H_5O)_2P(=O)O$, CH_3, H_B, H_C	H_B	4.71	−0.09	4.68	−0.22[b]		
		H_C	4.40	−0.31	4.45	+0.10		
		OCH_2		−0.34		+0.10		
		CH_2CH_3				+0.32		
	40	Vinyl CH_3		−0.09		+0.14		
	$Ph_2P(=O)O$, CH_3, H_B, H_C	H_B	4.75	−0.05	4.60	−0.29[b]	~1.0	
		H_C	4.37	−0.31	4.22	+0.10	2.5	
		Vinyl CH_3			1.90	+0.14		
	41							
	$PhP(=O)O(C_4H_9O)$, CH_3, H_B, H_C	H_B	4.70	−0.07	4.67	−0.20[b]		
		H_C	4.35	−0.27	4.35	+0.07		
		OCH_2	4.09	−0.28	4.03	+0.02		
		Vinyl CH_3	1.85	−0.09	1.85	+0.03		
	42							

TABLE II (*Continued*)

Origin	Compd	Isomer ratio	β-Vinyl H nmr: $-\delta_{Et_2O}$	$\Delta = \delta_{Et_2O} - \delta_{BF_3\text{-}Et_2O}$	$-\delta_{CCl_4}$	$\Delta = \delta_{CCl_4} - \delta_{C_6D_6}$	J_{POCCH}, Hz	Other data
 X = Cl, Br	 **12a**	*c*	5.66	−0.16	5.60	+0.05	2.5	Ir (CCl_4) 1667 cm^{-1}
	 **12b**	*c*	5.785	−0.035	5.77	−0.23	2.8	
7 + $ClP(=O)(OC_2H_5)_2$ →	**12a**		5.59 1.84 (vinyl CH_3)	−0.18 0.00	5.55 1.835	+0.03 +0.035		
	 **31a**	60	6.31	−0.19	6.13	+0.21	2.3	Ir (CCl_4) 1650 cm^{-1}
	 **31b**	40	6.56	−0.08	6.45	−0.25	2.8	
	 **32a**	97	6.36	−0.21	6.14	+0.17	1.6	Ir (CCl_4) 1625 cm^{-1}
	 **32b**	3	6.59	*d*	6.49	−0.23	2.8	
	 **15**		5.45	−0.14	5.39[e]	−0.24	2.2	^{31}P nmr +6.25 ppm
 **35**	 **37**		5.51	−0.15	5.38[e]	−0.32		
	 **43**		5.15	−0.22	5.18	−0.11 +0.09 (CH_2), +0.20 (CH_3)		Ir (film) 1695 cm^{-1}
	 **44**		5.54	−0.16	5.45	−0.30 +0.04 (CH_2), +0.24 (CH_3)		

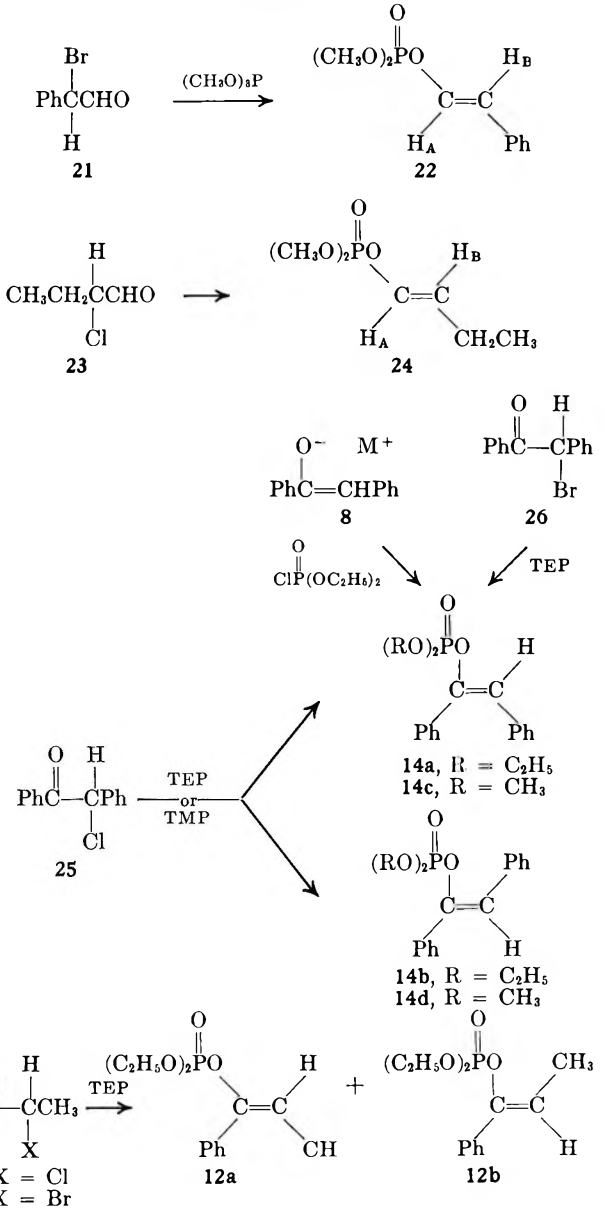
TMP 21 →	$(CH_3O)_2P(=O)O$	H_B	6.37	−0.26	6.32[f]	−0.06	1.6	J_{AB} = 12 Hz
	Ph	H_A		−0.02		−0.20		
	22							Ir (CCl_4) 1652 cm^{-1}
TMP 23 →	$(CH_3O)_2P(=O)O$	H_B	5.385	−0.32	5.38[f]	−0.01	1.4	J_{AB} = 12.3 Hz
	C_2H_5	H_A		−0.06		−0.13		
	24							
TMP 27 →	$(CH_3O)_2P(=O)O$	H_B	6.26 (70)	−0.23	6.14	+0.185	1.5	J_{AB} = 11.5 Hz
	Cl	H_A	6.87	−0.04	6.80	−0.04		
	28a							
	$(CH_3O)_2P(=O)O$	H_B	5.70 (30)	−0.30	5.605	+0.435	1.7	J_{AB} = 4.3 Hz
	Cl	H_A						
	28b							

[a] Vinyl phosphates **14a** and **14b** were recovered in unchanged isomeric ratio after removal of the BF_3 with $NaHCO_3$. [b] No crossover of the vinyl protons in going from CCl_4 to C_6D_6 was demonstrated by examining **39**–**42** in mixtures of the solvents as well as in the pure solvents. [c] Vinyl phosphates **12a** and **12b** are obtained in 1.6:1 or 2.3:1 ratio from the α-chloro and α-bromo ketone, respectively. [d] Signal too weak for accurate value to be established. [e] δ_{CCl_4} for the vinyl proton of cyclohexene is −5.68, using the convention[5a] which expresses downfield shifts from TMS as negative. This establishes a cis phosphate "Z" value of +0.30 ppm. [f] These compounds are used to establish a geminal phosphate "Z" value of −1.42 ppm.

of the enolate **8** or reaction of the bromo ketone **26** with TEP gives only **14a**.

The minor isomers **14b** and **14d** represent examples of compounds with β-vinyl protons which are trans to phosphate. These cases give small BF_3 shifts (−0.02 and −0.04 ppm) and $\Delta = \delta_{CCl_4} - \delta_{C_6D_6}$ shifts which are positive (+0.30 and +0.28 for **14b** and **14d**). By similar reasoning, the reaction of α-chloro- or α-bromopropiophenone (**29**, **30**) with TEP gives the *E*-vinyl phosphate **12a** as the major isomer (Scheme III). The

SCHEME III



C_6D_6 shift for the trans methyl group in **12a** is only +0.035, a much smaller value than trans β-methyl shifts reported in other vinyl systems.[21]

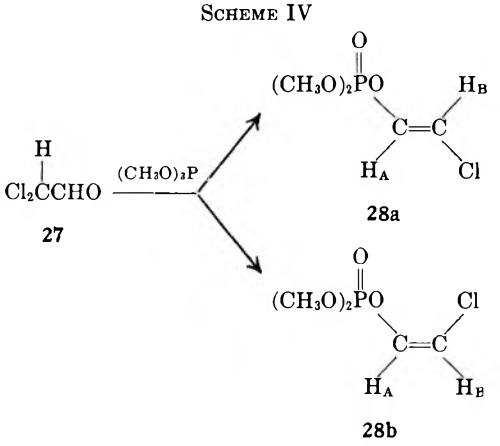
Vinyl phosphates bearing halogen atoms give ambiguous BF_3 shifts. Thus α,α-dichloroacetaldehyde (**27**) reacts with TMP to give 80:20 **28a** and **28b** (Scheme IV), as determined by J_{AB} (Scheme IV, Table II). The H_B protons of both isomers are deshielded by BF_3, however. The C_6D_6 shift is in the predicted manner, *i.e.*, H_{trans} is more shielded (+0.44) than is H_{cis} (+0.19). The situation is more complex for the iso-

TABLE III
CALCULATION OF VINYL PROTON NMR ABSORPTION IN VINYL PHOSPHATES

Compd	Vinyl proton (δ, CCl_4) Obsd	Calcd	Compd	Vinyl proton (δ, CCl_4) Obsd	Calcd
14a	6.33	6.34	**22**	H_A 7.08	7.08
14c	6.34			H_B 6.32	6.32
14b	6.69	6.59	**24**	H_A 6.32	6.43
14d	6.67			H_B 5.38	5.41
			28a	H_A 6.80	6.83
	H_B	4.91		H_B 6.14	6.02
11	5.21		**28b**	H_A 6.80	6.78
	H_C	5.16		H_B 5.605	5.82
12a	5.60	5.35	$(CH_3O)_2P(=O)O$, H, CH_3, CO_2CH_3	5.76[b]	5.47
			33a (major isomer, $J_{PH} \cong 1.5$ Hz)		
12b	5.77	5.60	$(CH_3O)_2P(=O)O$, CO_2CH_3, CH_3, H	5.47[b]	5.29
			33b (minor isomer, $J_{PH} \cong 0$ Hz)		
31a	6.13	5.96	^-O, $P(=O)O$, CN, ^-O, H_A, H_B		
31b	6.45	6.21	**34**	H_A 4.73 (D_2O)[c]	5.07 (D_2O)
				H_B 7.33 (D_2O)	7.22 (D_2O)
32a	6.14	5.93			
32b	6.49	6.18 (6.01)[a]	**40**	H_B 4.68	4.63
				H_C 4.45	4.45
15	5.39	5.39			

[a] Using Tobey's special values for crowded bromine.[5a] [b] Reference 26. [c] Reference 22.

SCHEME IV



meric diethyl 1-phenyl-2-bromovinyl phosphates (**31a** and **31b**) and the corresponding chloro compounds **32a**, **32b**. They are tentatively assigned the configurations shown in Table II on the basis of Tobey–Pascual shielding constants (Table III). The *E* isomer **31a** exhibits a larger negative BF_3 shift than does the *Z* isomer **31b** but the C_6D_6 shifts are reversed, *i.e.*, the apparent trans β-vinyl proton in **31b** is deshielded instead of being more shielded.[23] It was demonstrable that the addition of $BF_3 \cdot Et_2O$ caused no chemical change nor any isomerization of isomers under the conditions employed.

Prediction of Vinyl Proton Nmr Absorption in Vinyl Phosphates.—The assignment of vinyl phosphate stereochemistry by the above methods has led to the establishment of nmr shielding constants for a dialkyl phosphate group according to the methods of Tobey[5a] and Pascual[5b] as follows: geminal $OP(OR)_2$, −1.42; cis, +0.30; and trans, +0.50 ppm. These values are reasonably related to those reported for *O*-acetyl[5a] and are to be used with −5.27 ppm as the base value for ethylene (δ 5.27).[5a] These phosphate "*Z*" values correlate the nmr absorption of β-vinyl protons in vinyl phosphates of known stereochemistry fairly well (Table III). Where both vinyl phosphates are available, this method allows the assignment of *E* or *Z* configuration to known or unknown cases. The stereochemical assignments thus made are in agreement, in a number of cases, with those made by the use of BF_3 shifts. Confirmation of the assigned stereochemistry of the dimethyl 1-methyl-2-carbomethoxyvinyl phosphates **33a** and **33b** is found.[24] There is even good agreement for the cis isomer of 2-cyanovinyl phosphate dianion (**34**)[22] although we do not generally expect the same "*Z*" values to apply to other phosphorylated groups.

Long-Range Phosphorus Proton Coupling Constants.—The $J_{^{31}POCCH}$ coupling constants for vinyl H_B in all of the vinyl phosphates examined are in the range of 1.4–2.8 Hz, assuming first-order analysis. For the isomeric pairs **12**, **14**, **28**, **31**, and **32** (assuming that the stereochemical assignment is correct in each case) trans $J_{^{31}PH}$ > cis $J_{^{31}PH}$. The larger coupling constant is thus found for the "zigzag path" of the trans isomer.[25a,c]

(23) The reasons for the ambiguous behavior of the halovinyl phosphates are not clear. Vinyl halides do not differ in their nmr benzene solvent shifts from other olefins.[21] Chloro and bromo compounds are claimed not to coordinate with BF_3.[20b]

(24) T. R. Fukuto, E. O. Hornig, R. L. Metcalf, and M. Y. Winton, *J. Org. Chem.*, **26**, 4620 (1961).

(25) (a) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1966, pp 740, 741; (b) pp 735–739. (c) NOTE ADDED IN PROOF.—See E. Gaydou, J. Llinas, G. Peiffer, and A. Guillemonat, *Ann. Fac. Sci. Marseille*, **43**, 83 (1970), for relevant calculations.

The reported data for **33**, however, are $J_{^{31}PH} \cong$ 1.5 Hz for the cis β-vinyl proton in **33a** and *ca.* 0 for the trans vinyl proton in **33b** (based on ^{31}P nmr spectra),[25] in contradiction to our observations. In view of the complex nature of the factors influencing proton allylic coupling constants[25b,26] and since less is known about allylic phosphorus proton coupling, no generalization can safely be made.

Other Spectral Data for Vinyl Phosphates.—The ^{31}P nmr absorption of several vinyl phosphates is given in Table II.[27] The *Z* and *E* isomers of **14** were not sufficiently resolved at 24.29 MHz for an assignment to be made. The small positive shifts for **14c** and **15** are in accord with other vinyl phosphate data.[28] The ultraviolet spectra of **14a** and of the corresponding vinyl phosphinate **36** (see below) are more closely related to that of *cis*-stilbene (λ_{max} 280 nm) than that of *trans*-stilbene (λ_{max} 295 nm),[29] as expected.

Diphenyl Vinyl Phosphinates.—The reactions of α-halo ketones with ethyl diphenylphosphinate (**35**) lead, in many cases, to diphenyl vinyl phosphinates.[30] Preliminary studies indicate nmr behavior for these species similar to that of vinyl phosphates, as shown by **36** and **37** (Table II). The relationship of the stereochemistry of vinyl phosphate formation to the mechanistic pathways involved will be considered elsewhere.

Experimental Section[31]

All of the solvents used were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions were conducted under an atmosphere of prepurified nitrogen. Organic solutions were dried over magnesium sulfate. The reactions of α-bromopropiophenone, α-chloropropiophenone, α-bromobenzyl phenyl ketone, and α-chlorobenzyl phenyl ketone with TEP have been previously recorded.[3c]

Phosphorylation of Enolates. Kinetic Control Methods. Procedure A.—Potassium (0.99 g, 0.025 g-atom) was added to triphenylmethane (6.1 g, 0.025 mol) in glyme (50 ml). The resultant mixture was stirred at 22° for 24 hr to give a dark red solution. Acetophenone (2.50 g, 0.021 mol) was added until the red color was just discharged. Diethyl phosphorochloridate (8.63 g, 0.050 mol) was then added, and the resultant mixture was stirred at 22° for 30 min, cooled, and filtered. Vpc analysis (on 3 or 5% SE-30 on Chromosorb W at *ca.* 180°), with the aid of a calibration curve for the vinyl phosphate **11**, indicated that **11** (61%) and the ketophosphonate **16** (11%) were formed.

Procedure B.—*n*-Butyllithium (2.5 *M* in hexane, 0.0065 mol) was treated with triphenylmethane (0.0065 mol) in THF to give lithium triphenylmethyl at 0°. The ketone (propiophenone or benzyl phenyl ketone, 0.005 mol) was added by syringe *via* a serum cap until the solution was light pink. Diethyl phosphorochloridate (0.006 mol) was added rapidly at 0° and the reaction was kept at 0° for 1 hr. After removal of the solvent, nmr analysis of the resultant mixture ($CDCl_3$) gave product ratios using triphenylmethane as an internal standard.

Equilibrium Control Method. Procedure C.—Using procedure B, *n*-butyllithium (0.005 mol), triphenylmethane (0.0055 mol), ketone (0.006 mol), and diethyl phosphorochloridate (0.006 mol), the ketone was added to give a colorless solution which was kept at 0° for 60 min before phosphorylation.

In several cases, the reaction mixture, from procedure A mainly, was chromatographed on silica gel with benzene and ether–benzene as eluents to give vinyl phosphates as isolable products.

Attempted Reaction of an Enolate with Vinyl Phosphates.—A mixture of the potassium enolate of acetophenone (procedure A), from acetophenone (2.40 g, 0.020 mol) and diethyl cyclohexenyl phosphate (**15**, 4.68 g, 0.020 mol) was heated at reflux in glyme for 30 min and distilled to give **15** and two minor components (by vpc on 5% SE-30). Similar treatment of the above enolate with diethyl 1-phenylvinyl phosphate (**11**) gave only acetophenone and **11**.

Vinyl Phosphates.—Pertinent data are given in Tables II and III. The nmr spectra (CCl_4) were consistent with assigned structures, generally exhibiting δ 7.1–7.7 (m, 5 or 10, phenyl, when present), *ca.* 3.95 (m, 4, CH_2CH_3), *ca.* 0.82 (t, 3, CH_2CH_3) as well as vinyl absorption as in Table II, or (for dimethyl phosphates) 3.5 ppm (CH_3O).

Diethyl 1-phenyl-2-chlorovinyl phosphate (**31**): 73% from TEP and dichloroacetophenone; bp 140° (0.3 mm).

Anal. Calcd for $C_{12}H_{16}O_4ClP$: C, 49.58; H, 5.55. Found: C, 49.65; H, 5.57.

Diethyl 1-phenyl-2-bromovinyl phosphate (**32**): 91% from TEP and dibromoacetophenone; bp 140–145° (0.05 mm).

Anal. Calcd for $C_{12}H_{16}O_4BrP$: C, 43.01; H, 4.81. Found: C, 43.25; H, 4.90.

Dimethyl 2-phenylvinyl phosphate (**22**): 74% from 2-chloro-2-phenylacetaldehyde and TMP; bp 135–140° (0.75 mm).

Anal. Calcd for $C_{10}H_{13}O_4P$: C, 52.64; H, 5.74; P, 13.57. Found: C, 52.46; H, 5.62; P, 13.44.

Dimethyl 2-ethylvinyl phosphate (**24**): 11% from crude 2-chlorobutyraldehyde and TMP; bp 60–80° (0.6 mm); mass spectrum[32] (70 eV) *m/e* calcd for $C_6H_{13}O_4P$, 180.0559 (found, 180.0575).

Diethyl cyclopentenyl phosphate (**43**): 68% from TEP and 2-chlorocyclopentanone; bp 85–87° (0.1 mm) [lit.[33] bp 104–105° (1 mm)].

Diethyl cycloheptenyl phosphate (**44**): 74% from TEP and 2-bromocycloheptanone; bp 117–120° (0.1 mm); vpc (10% SE-30) one peak.

Anal. Calcd for $C_{11}H_{21}O_4P$: C, 53.22; H, 8.33. Found: C, 53.10; H, 8.49.

Diethyl 1-methylvinyl phosphate (**40**): 83% from TEP and chloroacetone; bp 90–91° (5 mm) [lit.[34] 65–66° (1.5 mm)].

Attempted Synthesis of the Diethyl Phosphate of 1-Hydroxy-1-halo-1,2-diphenylethane.—Treatment of the erythro bromohydrin **19** [from the reaction of *trans*-stilbene epoxide (**18a**) with HBr or from *trans*-stilbene, *N*-bromosuccinimide, NaOAc, and HOAc[35]] with diethyl phosphorochloridate and triethylamine (or with collidine), with $POCl_3$ and triethylamine, or with $POCl_3$ and triethyl phosphate (followed by ethanol for the latter two reactions) gave none of the desired phosphate **20** (Scheme II). Attempts at reacting **18a** with diethyl phosphate and *p*-TSA, or with diethyl phosphorochloridate and aluminum chloride,[36] were also unsuccessful.

Reduction of Dimethyl 1,2-Diphenylvinyl Phosphate.—Ammonia (100 ml, purified by distillation from Li wire) was added to a nitrogen-filled flask containing **14c,d** (3.04 g, 0.0100 mol) in anhydrous diethyl ether (20 ml) and *tert*-butyl alcohol (1.52 g, 0.0200 mol) at 22°. Lithium wire (0.14 g, 0.0200 g-atom) was added in pieces by means of an erlenmeyer flask connected with Gooch tubing. The ammonia was allowed to evaporate overnight. Then, after addition of saturated aqueous $NaHCO_3$ (100 ml) and diethyl ether (100 ml), the phases were separated. The organic layer, combined with an ether extraction (100 ml) of the aqueous layer, was washed with 1 *N* NaOH (100 ml), dried, filtered, and evaporated *in vacuo* to give *trans*-stilbene (1.73 g, 0.0096 mol, 96%); ir and nmr (CCl_4) were identical with those

(26) G. P. Newsoroff and S. Sternhell, *Tetrahedron Lett.*, 6117 (1968).

(27) Performed on a JEOLCO C-60H nmr spectrometer by Professor Grace Borowitz, Upsala College.

(28) F. Ramirez, K. Tasaka, N. B. Desai, and C. P. Smith, *J. Org. Chem.*, **33**, 25 (1968).

(29) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, pp 431–434.

(30) (a) I. J. Borowitz, E. W. R. Casper, and R. K. Crouch, *Tetrahedron Lett.*, 105 (1971); (b) H. Parnes and R. K. Crouch, Yeshiva University, unpublished results.

(31) The instrumental techniques used have mainly been recorded previously.[3c] More recent nmr spectra were recorded on a Varian A-60A spectrometer and infrared spectra were recorded on a Perkin-Elmer 257 infrared spectrophotometer.

(32) Mass spectra were kindly done by R. Foltz, Battelle Memorial Institute, on an AEI MS-9 mass spectrometer on NIH Contract 69-2226.

(33) B. A. Arbusov, V. S. Vinogradova, and N. A. Polezhaeva, *Dokl. Akad. Nauk SSSR*, **121**, 641 (1958); *Chem. Abstr.*, **53**, 1180 (1959).

(34) A. J. Speziale and R. C. Freeman, *J. Org. Chem.*, **23**, 1883 (1958).

(35) H. O. House, *J. Amer. Chem. Soc.*, **77**, 3070 (1955).

(36) R. W. Upson, *ibid.*, **75**, 1763 (1953).

of the genuine sample. A similar reaction but with ethanol (2 equiv), added 30 min after the Li, gave the same result. A reaction with excess Li (36 equiv) and *tert*-butyl alcohol (26 equiv, initially present) gave an oil whose nmr spectrum ($CDCl_3$) showed vinyl protons at δ 5.4, 5.7 but no aromatic absorption; *i.e.*, the phenyl rings were reduced to cyclohexyl groups. Reaction of 14c,d at −78° (Dry Ice–acetone bath) with Li (2 equiv) and methanol (initially present) gave phenyl benzyl ketone (33%) and no stilbenes.[37]

(37) This cleavage of a vinyl phosphate to the enolate of phenyl benzyl ketone, which is then protonated by methanol, is related to other cleavage reactions of enol phosphorylated species which are currently under investigation in our laboratory.[30a]

Registry No.—**11**, 1021-45-0; **12a**, 10409-51-5; **12b**, 10409-50-4; **14a**, 10409-53-7; **14b**, 10409-52-6; **14c**, 31327-09-0; **14d**, 31327-10-3; **15**, 4452-32-8; **22**, 31327-12-5; **24**, 31327-13-6; **28a**, 31327-14-7; **28b**, 31327-15-8; **31a**, 31327-16-9; **31b**, 31327-17-0; **32a**, 31327-18-1; **32b**, 31428-82-7; **36**, 31327-21-6; **37**, 30758-41-9; **38**, 31327-19-2; **39**, 31327-22-7; **40**, 5954-28-9; **41**, 1733-53-5; **42**, 31327-25-0; **43**, 30842-23-0; **44**, 31327-27-2.

Acknowledgment.—We are indebted to Professors Grace Borowitz, Bernard Miller, and Koji Nakanishi for stimulating discussions.

α-Anions. IV. Positional and Stereochemical Isomerization of 2- and 3-Unsaturated Carboxylic Acid Dianions[1a]

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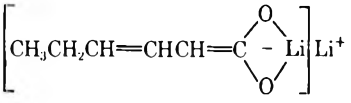
The stable dianions (carbanions of carboxylate salts) of the geometric isomers of 2- and 3-hexenoic acids were prepared and the nature of the carbanions was determined by deuteration and alkylation. Each of the four geometric anions, *i.e.*, *cis*- and *trans*-2-hexenoate dianions and *cis*- and *trans*-3-hexenoate dianions, on reprotonation gave 3-hexenoic acid exclusively. The results suggest the carbanion species of the 3-alkenoic acid salts to be more stable than the carbanion species of the 2-alkenoic acid salts. The geometric transformations that evolved provided further insights into the nature of the isomerizations. *trans*-2-Hexenoic acid gave a mixture of the cis-3 isomer (67%) and trans-3 isomer (33%), whereas *cis*-2-hexenoic acid gave the trans-3 isomer exclusively. The dianions from *cis*- and *trans*-3-hexenoic acids showed no indication of either positional or geometric isomerization since reprotonation regenerated the acids unchanged. A mechanistic scheme is described in terms of a polarized dianion of the following structure to explain these phenomena.



The isomeric 3-olefinic acids I and 2-olefinic acids II, have been reported by Linstead and Noble[2] to equilibrate (eq 1) in the pure state and in organic solvents,

$$\underset{\text{I}}{RCH{=}CHCH_2COOH} \rightleftharpoons \underset{\text{II}}{RCH_2CH{=}CHCOOH} \quad (1)$$

water, and alkaline solutions. The acids were induced to isomerize at elevated temperatures (100–200°), and the rates were greatly accelerated at these temperatures by alkali. The 2-olefinic isomer II was produced in the equilibrium as the thermodynamically favored acid, *i.e.*, the proportions of 2-olefinic to 3-olefinic were 70:30 for the *n*-hexenoic and *n*-pentenoic acids and 98:2 for *n*-butenoic acid.

In a continuation of our studies on the chemistry of α-metalated carboxylic acids ($RCHLiCOOLi$),[3-5] we have examined the carbanions derived by reaction of lithium diisopropylamide with isomeric 2- and 3-alkenoic acids. Crotonic acid produced a dianion that on quenching with hydrochloric acid yielded 3-butenoic acid quantitatively and exclusively. This unexpected shift of the conjugated double bond into the β,γ position is counter to the results reported for the thermodynamic equilibrium of the isomeric acid pair for which α,β-alkenoic acid predominates.[6] Since butenoic acid isomers provide limited stereochemical information, the longer chain 2- and 3-hexenoic acids were chosen for a more detailed investigation of the transformation.

The dianions of cis and trans isomers of 2- and 3-hexenoic acids were prepared by reaction of the individual geometric isomers with lithium diisopropylamide in tetrahydrofuran (THF) solution at 0°; the solution was then quickly warmed to room temperature and allowed to stir for 30 min.[3,5] The dianions were quenched with dilute hydrochloric acid and the recovered acids, after their conversion to methyl esters with diazomethane, were examined by glpc for determinations of geometric and positional isomerization. The *trans*-2-hexenoic acid (III) gave a mixture of 67% *cis*-3-hexenoic acid (IV) and 33% *trans*-3-hexenoic acid (V) in a combined yield of 98% (eq 2).[7] Prolonged heating (4 hr) of this dianion mixture at 45–50° induced no change in its isomeric composition. Similar treatment of the *cis*-2-hexenoic acid (VI) gave *trans*-3-hexenoic acid (V) exclusively (eq 3). The complete isomeriza-

(1) (a) Presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28–April 2, 1971. (b) Eastern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) R. P. Linstead and E. G. Noble, *J. Chem. Soc.*, 610 (1934).

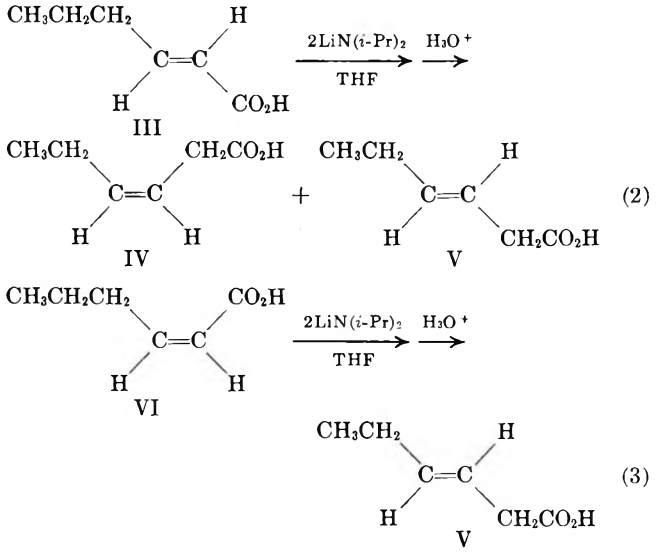
(3) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **35**, 262 (1970).

(4) P. E. Pfeffer and L. S. Silbert, *Tetrahedron Lett.*, 699 (1970).

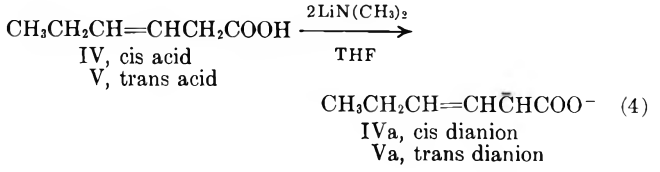
(5) P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr., *J. Org. Chem.*, in press.

(6) A photochemical transformation of crotonic acid to 3-butenoic acid has previously been reported to occur in 59% yield after prolonged irradiation and equilibration of crotonic and isocrotonic acids: P. J. Kropp and H. J. Krauss, *ibid.*, **32**, 3222 (1967).

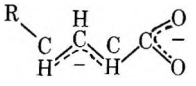
(7) A cis,trans mixture of α,β-unsaturated acids has been reported to isomerize photochemically to their β,γ isomers composed of a cis/trans ratio of 0.5: R. R. Rando and W. von E. Doering, *ibid.*, **33**, 1671 (1968).



tion of 2-hexenoic acid isomers to 3-hexenoic acid isomers reflects the relative stability of the carbanions of the latter acids as the thermodynamically more stable forms. Further demonstration of this relationship is provided by the observation that *trans*-3-hexenoic acid (V) and *cis*-3-hexenoic acid (IV) are metalated to the stable *trans*-3-hexenoate dianion (Va) and *cis*-3-hexenoate dianion (IVa), respectively, with no indication of isomerization to the 2 isomers nor change in stereochemical purity (eq 4). Deuterium oxide quenching of the dianions ob-



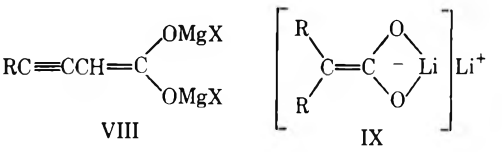
tained from each of the four isomers quantitatively introduced one deuterium atom at the α position. These results suggested that the negative charge of the carbanion involves only the α-carbon position without its participation in delocalization as expected for a resonance hybrid of the allylic anion of structure VII.



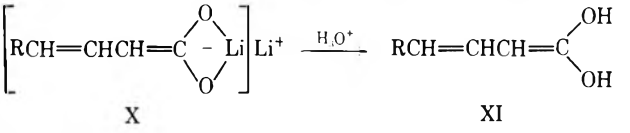
VII

Alkylation with CH_3I of the dianion derived from each isomer gave exclusive substitution at the 2-carbon position. In the case of *trans*-2-hexenoic acid, there were obtained the two monomethylated products, *cis*-2-methyl-3-hexenoic acid (57%) and *trans*-2-methyl-3-hexenoic acid (29%) and the dimethylated product mixture of the cis and trans forms of 2,2-dimethyl-3-hexenoic acid (14%). The ratio of *cis*- and *trans*-monomethylated product is in accord with the ratio observed for the carbanions prior to alkylation. *cis*-2-Hexenoate dianion is methylated to a mixture of *trans*-2-methyl-3-hexenoic acid (85%) and 2,2-dimethyl-3-hexenoic acid (15%) (geometric configuration not determined). Chain methylation of *cis*-3-hexenoate and *trans*-3-hexenoate dianions resulted in formation of their respective cis and trans isomers of 2-methyl-3-hexenoic acid with no evidence of any stereochemical change.

Ivanoff, *et al.*,[8] have acquired spectral evidence for the organomagnesium salts of 3-acetylenic acids which they depicted as a conjugated triple–double bond structure (VIII) and Creger[9] has suggested a similar delocalized "aci-carboxylate" (IX)[10] which he termed an



"ate" structure, for the metalated species of saturated acids. A corresponding alkene "aci-carboxylate" (X) representing the dianion intermediate common to both 2- and 3-hexenoic acids may assist in explaining the



stability of the dianion as well as the resulting products obtained after protonation.[11] Since reprotonation gives rise only to 3-hexenoic acids, this is interpreted as indicating little conjugative interaction between the π bond at C_3–C_4 and the strongly polarized π bond at C_1–C_2. Reprotonation of X would be effected at the carboxylate grouping to generate the enol form of the acid (XI) that would prototropically shift only to the α carbon.[11a]

The stereochemical transformations of reactions 2 and 3 are relevant for their geometric differences, since both geometric isomers arise only from *trans*-2-hexenoic acid (reaction 2) in the course of the positional shift. *cis*-Allylic anions are reported to be the more stable thermodynamic anion species for the isomerization of terminal olefins to internal olefins.[12,13] Also, the specific base-catalyzed isomerization of simple olefins *via* the intermediate carbanions has been accorded an explanation by Kloosterziel and Van Drunen.[14] In terms of their concept for trans-to-cis isomerizations the *cis*-alkylallylic anions are more stable than the trans isomers; for cis-to-trans isomerizations, an all-cis conformation in the anion intermediate is prevented by steric hindrance. Although their interpretations serve as an explanation for simply constituted olefins, they are inadequate for rationalizing the results observed for the more complicated structures of our polar substituted olefinic systems. For example, application of the simple allylic concept to the isomerization of *trans*-2-hexenoate

(8) D. Ivanoff, B. Jordanov, and B. Blagoev, *Naturwissenschaften*, **51**, 286 (1964).

(9) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967).

(10) The designation "aci-carboxylate" indicates that the dianion structure is the salt of the enol form of the parent acid. This enolization corresponds to the nitro-aci–nitro relationship.

(11) Efforts to characterize these unsaturated dianions by nmr analysis were unsuccessful because of the high degrees of aggregation. The molecular weight averages determined by ultracentrifugation were in the range of 8000–30,000. The tetrahydrofuran solutions exhibited goth a Tyndall effect and fluorescence.

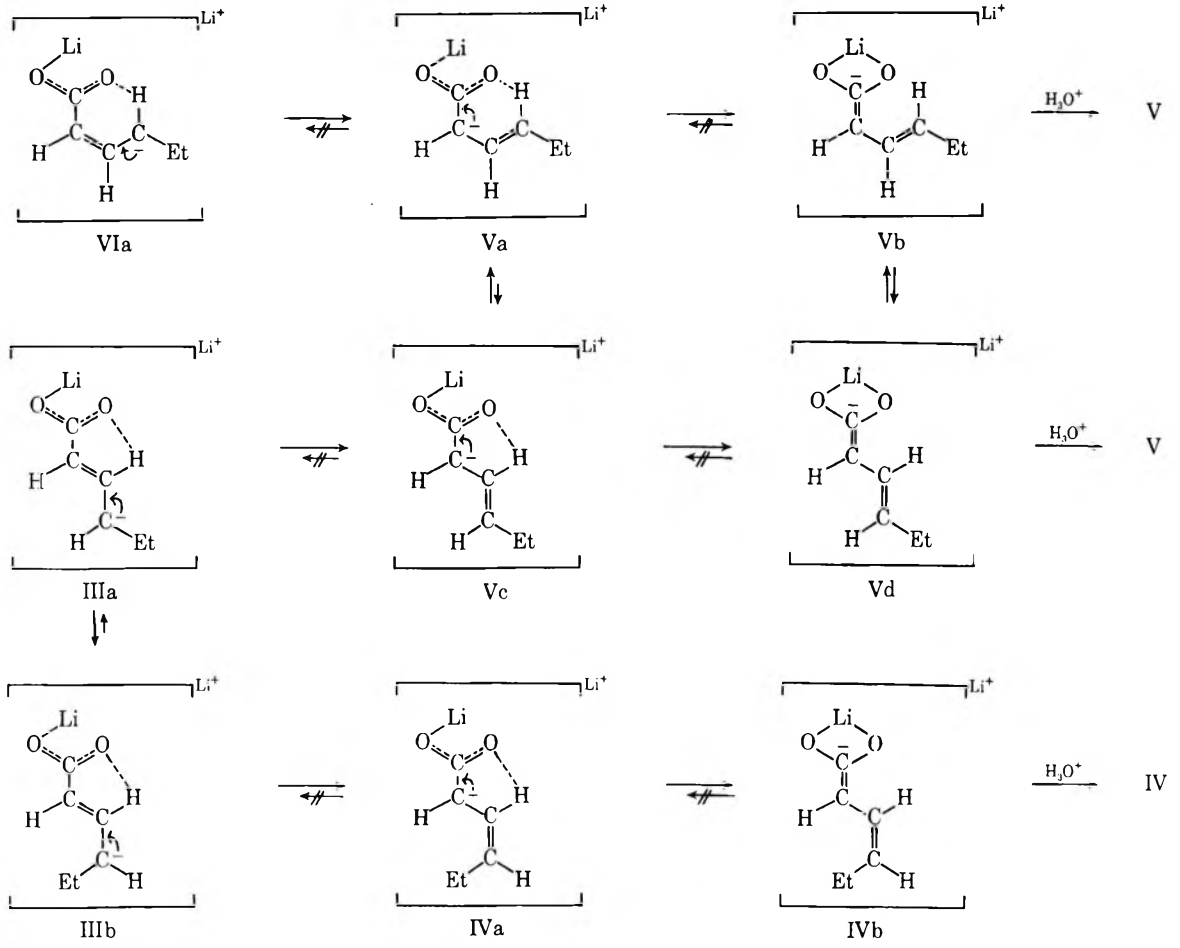
(11a) NOTE ADDED IN PROOF.—Since submission of this paper a recent investigation into the nature of the dianion derived from 2-methyl-3-phenylpropionic acid using nmr has indicated the structure to be consistent with the enolic form, $\mathrm{PhCH_2}(\mathrm{CH_3})\mathrm{C}=\mathrm{C}(\mathrm{OLi})(\mathrm{OLi})$ (P. L. Creger, private communication). In a recent study, Y. N. Kuo, F. Chen, and C. Ainsworth, *Chem. Commun.*, 136 (1971), trapping of the dianions derived from various carboxylic acids with trimethylsilyl chloride gave rise to ketene bis-silyl acetals, $R_1R_2C{=}C(OSiMe_3)_2$, thus substantiating the localization of charge on oxygen.

(12) S. Bank, A. Schriesheim, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **87**, 3244 (1965).

(13) S. Bank, *ibid.*, **87**, 3245 (1965).

(14) H. Kloosterziel and J. A. A. Van Drunen, *Recl. Trav. Chim. Pays-Bas*, **89**, 37 (1970).

SCHEME I



dianion leads to the conclusion that only *cis*-3-hexenoic acid should be the expected product whereas 67% cis and 33% trans isomers of 3-hexenoic acid are in fact obtained. In addition, if the 2-hexenoate and 3-hexenoate dianions were freely interacting through common allylic anion species, a change in the stereochemistry would be anticipated whereas none is observed. A proposed sequence of transformations for each isomer is depicted in Scheme I.

The salient features underlining the proposed scheme take into account the following generalizations: (a) prior to carbanion formation, the electronegative carboxylate group may stabilize specific conformations by formation of hydrogen bonded five-membered and six-membered quasi rings for which the six-membered rings are more stable; (b) after carbanion formation, the "aci-carboxylate" structure stabilizes the anion by formation of a polarized olefin; (c) unsaturated carbanions that are capable of conjugation with the aci form are stabilized by charge distribution onto the electronegative group;[15] and (d) the resonant allylic anion structure (XII) serves inadequately as a representation of the incipient allylic anion owing to formation of a stable "aci-carboxylate."

XII

trans-3-Hexenoate (Va) and *cis*-2-hexenoate (VIa) salts may each maintain the six-membered quasi ring during proton abstraction and anion migration without undergoing conformational changes. The *trans*-3-hexenoate dianion (Va) would shift directly to the trans-ene aci-carboxylate (Vb) whereas the *cis*-2-hexenoate isomer (VIa) would transiently pass through the *trans*-3-hexenoate (Va) stage in formation of Vb and thereby protonate to the same product, trans-3-hexenoic acid (V).

cis-3-Hexenoate dianion (IVa) may exist in only one stable quasi-ring structure, a five-membered ring that would consequently pass directly to the cis-ene aci-carboxylate (IVb) that reprotonates to *cis*-3-hexenoic acid (IV) exclusively.

trans-2-Hexenoate dianion may form two quasi-five-membered ring conformations (IIIa and IIIb), the relative amounts of each being dependent upon their respective stabilities; of the two conformations, IIIb (cis,-trans) and IIIa (trans,trans), the latter is reported to be the less stable type in the corresponding unsubstituted olefinic system.[14] Conformational isomer IIIb would proceed through the cis-3 stage IVa to the cis-ene aci-carboxylate (IVb) in formation of *cis*-3-hexenoic acid (IV) (67%). The other conformer (IIIa) would pass through the *trans*-3-enoate stage (Vc) to produce the trans-ene aci-carboxylate (Vd) that finally reprotonates to *trans*-3-hexenoic acid (V) (33%).

Experimental Section

Reagents.—Tetrahydrofuran was dried over sodium and distilled from a ketyl solution (sodium and benzophenone). Diisopropylamine was distilled from calcium hydride prior to use.

(15) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press New York, N. Y., 1965, p 205.

n-Butyllithium was purchased from Foote Mineral Co.[16] in 1.6 *M* hexane solution.

trans-2-Hexenoic and *trans*-3-hexenoic acids were obtained commercially, the former recrystallized and the latter distilled to 99+% purity. *cis*-2-Hexenoic acid was prepared by the method of Rappe and Adeström.[17] *cis*-3-Hexenoic acid was prepared by the rearrangement of *trans*-2-hexenoic acid using lithium diisopropylamide (see below).

Equipment.—All nmr spectra were recorded on a JEOLCO C-60 spectrometer in CCl_4. All shifts are reported relative to tetramethylsilane. Ir spectra were recorded on a Perkin-Elmer IR-457 spectrometer.

Anionic Rearrangement of Hexenoic Acids.—Anhydrous THF (20 ml) and diisopropylamine (1.7 g, 0.0174 mol) were added to a dry, nitrogen-flushed flask and maintained under a nitrogen atmosphere throughout the reaction. *n*-Butyllithium in hexane (8.45 ml of 1.6 *M*, 0.0176 mol) was added to the magnetically stirred solution followed by addition of hexenoic acid (1.0 g, 0.00875 mol), each added at a controlled rate for maintaining the temperature below 0°. The solution was stirred for 30 min at room temperature, quenched with 10% HCl, and extracted with petroleum ether (bp 30–60°). The extracts were dried, the solvent was evaporated, and the mixtures of acids were converted to methyl esters with ethereal diazomethane. The products were analyzed by glpc (4-ft column, 10% $AgNO_3$–ethylene glycol) at 65° column temperature. The four methyl hexenoate isomers were readily separated at their indicated retention times: methyl *cis*-2-hexenoate (3.5 min), methyl *trans*-2-hexenoate (4 min), methyl *trans*-3-hexenoate (16 min), and methyl *cis*-3-hexenoate (32 min). These esters were subsequently trapped for their complete spectral analysis and comparison with authentic samples.

The hexenoic anion solutions prepared as above were quenched with D_2O (20 ml) and acidified with dilute HCl. The acids were extracted and the solutions dried and evaporated. The extent of deuterium incorporation in the 2 position was determined by nmr and the total deuterium content confirmed by mass spectral analysis.

Alkylations of Anions with Methyl Iodide.—Alkylation was carried out by the addition of methyl iodide (1.5 mol per mole of acid). The alkylations were complete within 90 min. Washings and isolation of products were the same as described above. The acids were converted to methyl esters with diazomethane and analyzed by glpc (4-ft column, $AgNO_3$–ethylene glycol). These esters were trapped and fully characterized with the exception of the isomeric methyl 2,2-dimethyl-3-hexenoates (cis and trans).

Spectral Data.—Spectral data for *trans*-2-, *trans*-3-, *cis*-2-, and *cis*-3-hexenoic acids and methyl esters have been documented.[17,18]

Methyl *cis*-2-methyl-3-hexenoate: nmr (CCl_4) δ 5.30 (m, 2, olefinic), 3.55 (s, 3, OCH_3), 3.22 (d, 1, α CH), 2.02 (m, 2, allylic CH_2), 1.15 (d, 3, CH_3), 0.95 (t, 3, CH_3); ir (CCl_4) 1740 cm^{-1} (C=O), no bands in 970-cm^{-1} region; mass spectrum (70 eV) *m/e* 142.

Methyl *trans*-2-methyl-3-hexenoate: nmr (CCl_4) δ 5.40 (m, 2, olefinic), 3.59 (s, 3, OCH_3), 2.95 (m, 1, α CH), 2.05 (m, 2, allylic CH_2), 1.15 (d, 3, CH_3), 0.98 (t, 3, CH_3); ir (CCl_4) 1740 (C=O), 968 cm^{-1} (trans double bond); mass spectrum (70 eV) *m/e* 142.

Isomeric mixture (cis and trans) of methyl 2,2-dimethyl-3-hexenoate: nmr (CCl_4) δ 5.4 (m, 2, olefinic), 3.55 (s, 3, OCH_3), 2.05 (m, 2, allylic CH_2), 1.2 (s, 6, CH_3), 1.0 (t, 3, CH_3); ir (CCl_4) 1740 (C=O), 968 cm^{-1} (trans double bond); mass spectrum (70 eV) *m/e* 156.

Registry No.—Methyl *cis*-2-methyl-3-hexenoate, 31599-11-8; methyl *trans*-2-methyl-3-hexenoate, 31599-12-9; methyl *cis*-2,2-dimethyl-3-hexenoate, 31599-13-0; methyl *trans*-2,2-dimethyl-3-hexenoate, 31599-14-1; *cis*-2-hexenoate dianion, 31599-17-4; *trans*-2-hexenoate dianion, 31599-18-5; *cis*-3-hexenoate dianion, 31599-15-2; *trans*-3-hexenoate dianion, 31599-16-3.

Acknowledgment.—The authors are grateful to Thomas F. Kumosinski for the ultracentrifuge determination of the dianion aggregates and to C. J. Dooley for the mass spectral analyses.

(16) Reference to a particular manufactured product does not constitute a recommendation by the U. S. Department of Agriculture over similar products not mentioned.

(17) C. Rappe and R. Adeström, *Acta Chem. Scand.*, **19**, 383 (1965).

(18) A. F. Mabrouk, H. J. Dutton, and J. C. Cowan, *J. Amer. Oil Chem. Soc.*, **41**, 153 (1964); (b) E. N. Frankel, E. Selke, and C. A. Glass, *J. Amer. Chem. Soc.*, **90**, 2446, (1968).

Elements of Stereoisomerism and Prostereoisomerism[1]

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The elements of stereoisomerism, such as centers of stereoisomerism, which are used to specify the differences between stereoisomers can be tested for chirality by two reflection tests. These tests allow one to determine (a) whether the description of the configuration of an element requires reference to a chiral object, and (b) whether the element can or cannot contribute to the chirality of a molecular model. Definitions of the various chiral (*e.g.*, chiral centers) and achiral elements are proposed which are based on both reflection tests. Additional steric elements must be defined if all atoms and groups within a molecule that can be distinguished by chemical or physical tests are also to be distinguished in chemical discourse. These are named elements of prostereoisomerism and are defined by relating them to the corresponding elements of stereoisomerism. Prochiral centers constitute an important class of such elements. The prochirality concept is also applied to achiral configurations.

In developing the sequence rule procedure for specifying molecular chirality, Cahn, Ingold, and Prelog used as their steric elements the center, axis, and plane and on occasion the conformational helix.[2] They considered two types of the center, axis, and plane (the chiral and the pseudoasymmetric) but did not provide an explicit definition of these categories. Following this approach one of us[3] introduced the concept of prochiral elements and defined these by relating them to the cor-

(1) (a) Supported in part by Grants AM 9105 and K6-AM-14367 from the National Institutes of Health (H. H.), and GB 12428 from the National Science Foundation (K. R. H.). (b) The study was undertaken as a result of discussions by the Panel on Stereonomenclature of the Office of Biochemical Nomenclature, National Academy of Sciences–National Research Council (current panel membership: S. Englard, K. R. Hanson, H. Hirschmann, S. J. Kiehl, and G. J. Schroepfer, Jr.; corresponding members: D. Arigoni and W. Klyne) and its predecessor, the NAS–NRC Subcommittee on Biochemical Nomenclature. Our preliminary conclusions were presented at a IUPAC–IUB meeting at the Ciba Foundation in London (1968) and in greater detail at a Table Ronde Roussel in Paris (1970).

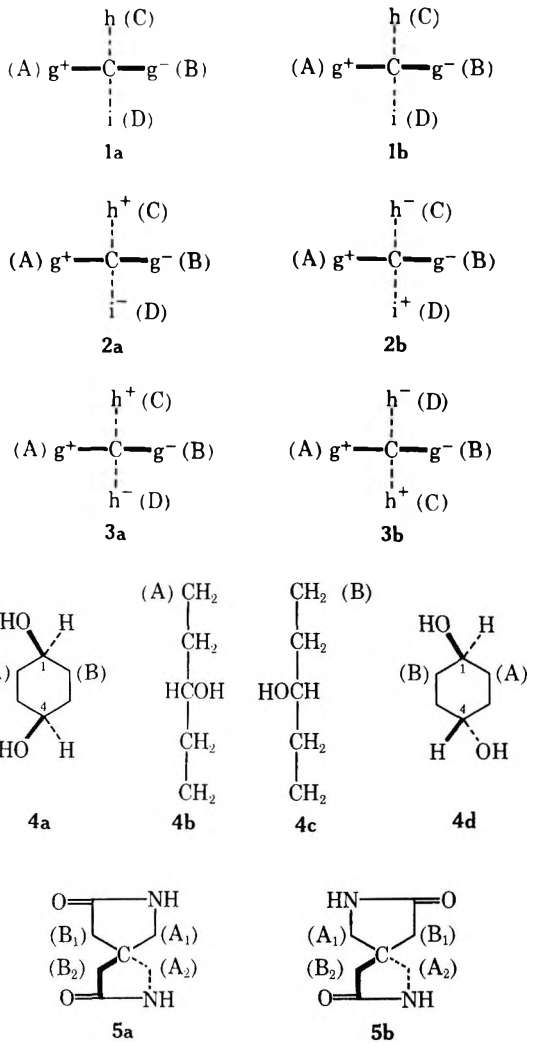
(2) R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385, 511 (1966).

(3) K. R. Hanson, *J. Amer. Chem. Soc.*, **88**, 2731 (1966).

responding chiral and pseudoasymmetric elements. The necessity for revising the definition of prochirality became clear when it was recognized that two fundamentally different approaches to factorizing a molecule into its steric elements had been employed. Cahn, *et al.*,[2] emphasized that the factorization step is prior to and independent of the use of the sequence rule. On the other hand, Hanson[3] made the sequence rule the final arbiter in deciding when two ligands at a center were alike or distinct. Although in the vast majority of cases the proper classification of a steric element is quite obvious, enough ambiguous cases were encountered to prompt us to search for precise definitions that would be independent of any specific system of nomenclature.

Some of the problems may be illustrated by quoting a passage from van't Hoff's "Chemistry in Space."[4] "In the first place, with regard to asymmetry, of course no carbon atom situated in a closed chain can be combined with four different groups, but if it does not possess a plane of symmetry it will still be asymmetric." If a carbon atom is to be regarded as asymmetric if it is joined to four different groups or if it does not lie in a plane of symmetry, we need to know which criterion governs when there is a conflict between these definitions. This is the case if two of the ligands form an enantiomeric pair as in Cg^+g^-hi (**1a**).[5] Those who stressed the difference between the four ligands have called the central carbon atom asymmetric;[6,7a] Werner[8] spoke of pseudoasymmetry to distinguish this case from those having "wirklich asymmetrische Kohlenstoffatome," *i.e.*, those with four ligands that were either materially or constitutionally distinct; Wittig[9a] called attention to the plane of symmetry and found that such a carbon atom is neither asymmetric nor "vorgetäuscht asymmetrisch." If we replace one or both of the achiral ligands (h, i) of **1** by chiral ones (as, *e.g.*, in **2a**) we lose the plane of symmetry. The recently published IUPAC rules[10] classify the central carbon atom of $Cg^+g^-h^+i$ as pseudoasymmetric, whereas Eliel[11] stated that it could be asymmetric. Werner called attention to case **3a** and, consistent with his definition, classified it as pseudoasymmetric. The IUPAC document also comments on this case, points out that the *molecule* is chiral, but the definitions given do not allow one to classify the central carbon as either asymmetric or pseudoasymmetric.

Both Werner[8] and the IUPAC[10] rules base their distinction between asymmetric and pseudoasymmetric carbon atoms on the nature of the difference between ligands. In order to decide whether two ligands are equivalent, enantiomeric, or otherwise distinct we must



have a clear understanding of what is meant by ligand. As the quotation from van't Hoff indicates, the meaning of ligand is not obvious if it is joined to the ligating atom by more than one bond. Wittig[9b] suggested that the bidentate ligand of an asymmetric carbon atom that is located in a ring could be split into two different halves, but used larger fragments on other occasions.[9c] The size of ligands attached to a chiral carbon atom also varies when they are compared for purposes of determining their sequence rule priorities:[2] exploration of a ligand stops when a difference has been found, but this process may require a return to the chiral atom whose ligands are being examined. Also no fixed terminus of a ligand was set when, for the purpose of determining asymmetric carbon atoms, the term group was defined[10] as "the series of atoms attached to one bond."

A definition of the asymmetric carbon atom with wider scope than the traditional ones was given by Mislow[7b] when he described it as an atom to which four substituents are attached which differ in the sense that an exchange of any two gives a new stereoisomer. According to this definition the carbinol carbons of 1,4-cyclohexanediol (**4a**) and the central carbon atoms of **5a**–**7a**[12] are asymmetric. Clearly this use of the term is unrelated to the way the space around these carbon atoms is occupied, as C-1 of cyclohexanediol lies in a plane of symmetry and the central atoms of

(4) J. H. van't Hoff, "Chemistry in Space," J. E. Marsh, Ed., Clarendon Press, Oxford, 1891, p 115.

(5) Throughout this paper simple lower case letters (g, h, ...) are used if the ligands have a plane of symmetry, and the symbols g^+ and g^-, etc., for a pair of enantiometric ligands. Capital letters (A, B, ...) signify proximal atoms as defined in [3] and the statement that follows [3].

(6) G. W. Wheland, "Advanced Organic Chemistry," 2nd ed, Wiley, New York, N. Y., 1949, p 192.

(7) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966: (a) p 91; (b) p 25; (c) p 50; (d) p 116.

(8) A. Werner, "Lehrbuch der Stereochemie," G. Fischer, Jena, 1904, p 28.

(9) G. Wittig, "Stereochemie," Akademische Verlagsgesellschaft, Leipzig, 1930: (a) p 88; (b) p 69; (c) p 91.

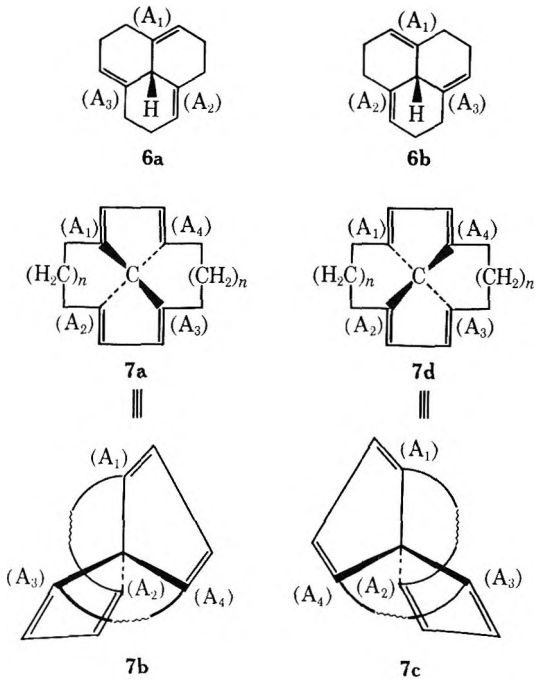
(10) IUPAC 1968 Tentative Rules, Section E. Fundamental Stereochemistry, *J. Org. Chem.*, **35**, 2849 (1970).

(11) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 29.

(12) Examples similar to or identical with structures discussed by Cahn *et al.*[2]

5–7 lie on one or more axes of rotational symmetry. With compound 7 in particular where all four atoms directly linked to the center are homotopic[13a] (they are superposable by operations of rotational symmetry), we face the question as to the nature of the difference between the substituents that allows us to obtain the enantiomer 7c from 7b by an exchange. In spite of its simplicity, Mislow's definition does not seem to be a suitable basis for a general definition of the chiral center. It can be extended to other tetrahedral atoms or to pyramidal triligated atoms. However, it seems inapplicable to trigonal carbon atoms, or to tetragonal or octahedral centers unless one wishes to call any center chiral that gives rise to stereoisomerism.

It is clear from this brief survey that there is no agreement among chemists on what constitutes an asymmetric carbon atom and that we shall need a general principle rather than *ad hoc* rules if we wish to define a chiral center.



A. Steric Centers

1. Centers of Stereoisomerism and Their Ligands. —A major purpose of the factorization of a structure into its steric elements is the development of an efficient procedure for the distinction of stereoisomers.[14] It seems appropriate therefore to begin with a more general concept than chiral center, namely a center of stereoisomerism. This we define according to the following exchange test.

(13) (a) As set forth in greater detail elsewhere,[13b] groups or atoms that are part of the same molecule and are indistinguishable in any chemical or physical test can be superposed by an operation of gyrosymmetry; such groups are called homotopic. The principal operations of gyrosymmetry are operations of rotational symmetry (C_n) and of torsional symmetry and their combinations. Groups (or atoms) that fail these superposition tests for steric reasons alone are called stereoheterotopic and may be subdivided into those that are enantiotopic and those that are diastereotopic. These subclasses were defined by Mislow and Raban,[13c] who initiated this form of description. (b) H. Hirschmann and K. R. Hanson, *Eur. J. Biochem.*, in press. (c) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

(14) Consistent with Mislow's definition,[7c] we call two different chemical species stereoisomers if their atoms are identically connected but differ in their distribution in space, and if these species are not readily interconverted under the conditions under which their difference is being established.

[1] **Centers of Stereoisomerism**

[1a] An atom is at a *general* center of stereoisomerism if a stereoisomer can be produced by separating the central atom from its ligands and reconnecting them in such a manner that an exchange in the positions of two atoms directly linked to the center takes place.[15]

[1b] A general center of stereoisomerism is *improper* if the same isomer that can be obtained by the exchange operation [1a] can also be realized by severing only one link to an adjacent atom and by reestablishing the link after a rotation.

[1c] A general center of stereoisomerism is *proper* if the stereoisomer can only be obtained by the exchange operation [1a]. Throughout this paper use of the words "center of stereoisomerism" without qualification will mean that the center is proper.

The central carbon atom of 1 and either of the olefinic carbon atoms in ghC=Cij are general centers of stereoisomerism, but the only proper center is that of 1; an exchange of the g and h ligands at the olefinic carbon, *e.g.*, would yield the same isomer as would be obtained by severing the double bond and by reconnecting the parts after the =Cij fragment has been rotated by 180°. This second way of isomerization is, of course, equivalent to a conceptual torsion of the double bond. Such improper centers of stereoisomerism will be considered in section B.

In the exchange operation [1a] an unused bonding orbital may be regarded as the equivalent of a bond. Occasionally (23) the exchange would result in an isomeric structure with prohibitive strain, whereas a realizable stereoisomer would result if the configuration at one or more other centers were also changed. Such an atom is also called a center of stereoisomerism, a designation which may be qualified, if desired, by the term interdependent.[16]

The exchange operation which produces stereoisomers allows one to determine how ligands ought to be defined for the purposes of factorization. In order not to prejudice the case by prior usage or by usage with different objectives, we shall speak of factorization ligands (abbreviated as *f*-ligands). If the compound is acyclic the *f*-ligands are simply the structures that result if all bonds to the central atom are broken, because these are the pieces that are reconnected to the center in a differ-

(15) (a) This definition is fundamentally similar to that given by McCasland[15b] for a stereogenic atom: "an atom (usually carbon) of such nature and bearing groups of such nature that it can have two non-equivalent configurations." Our definition is not limited to atoms that, like carbon, allow only two configurations. We are not using McCasland's term because we wish to distinguish between centers of stereoisomerism and of prostereoisomerism and find that the etymology of stereogenic fits one of these categories as well as the other. (b) G. E. McCasland, "A New General System for the Naming of Stereoisomers," a pamphlet available from the Chemical Abstracts Service, Columbus, Ohio 43210.

(16) In rare instances where the configuration of two centers cannot be independently altered, the exchange of bonds fails to produce a stereoisomer (*e.g.*, at C-2 and C-3 in 2,3-epoxysuccinic acid anhydride), but the superposition of the model before and after the bond exchange can be accomplished *only* if the center to be examined (*e.g.*, C-2) in the original model is in superposition with a different center (C-3) of the model after the exchange. Clearly, the designation of such a compound does not require the identification and steric description of such centers. However, the exchange test [1] reveals the nature of the steric difference between C-2 and C-3 and justifies their classification as "centers of intramolecular stereoisomerism." Their recognition as such and treatment as ordinary centers of stereoisomerism in nomenclature would provide a way for their differentiation by conventional terms (2*R*,3*S* in the example given).[13b]

ent manner when the stereoisomer is obtained. If we apply this to **4a**, H and OH are *f*-ligands of C-1. This is a center of stereoisomerism because we obtain the trans isomer by exchanging H and OH. We can conduct an analogous operation with a ring ligand if we give it a sense of direction. It may either start with A and end with B or *vice versa*. If the ligand starts with A, we shall call A the proximal atom. We can conduct an exchange if we reconnect in such a way that the proximal atom A takes the place originally occupied by B and *vice versa*. This again gives the trans isomer (**4d**). In obtaining it we have conceptually replaced the bidentate ligand by two *f*-ligands (**4b**, **4c**), with the proximal atoms A and B, respectively, and have exchanged these *f*-ligands. It follows that two *f*-ligands are identical only if they can be superposed in such a way that the positions of the two proximal atoms coincide. Such a superposition is not possible here; the two *f*-ligands are enantiomeric. Therefore, we define:

[2] **Factorization Ligands.**—The *f*-ligands of an atom are the structures that result (aside from the central atom) from the severance of all bonds leading to the atom. This cleavage is not to cause or allow any change of configuration in the ligands. In separating an *n*-dentate ligand, the cleavage can be initiated in *n* different ways. All of these are considered and in each case the first atom separated, the *proximal atom*, is held to be distinct from the $n - 1$ other distal atoms. This distinction is maintained when the *n* separated *f*-ligands are compared in order to determine whether they are superposable, enantiomeric, or otherwise distinct.

It follows from [1c] that stereoisomers at a center of stereoisomerism differ in the spatial distribution of the proximal atoms of this center. It is useful, therefore, to classify the proximal atoms as equivalent or nonequivalent, as this will allow us to determine when their exchange can produce a stereoisomer. Proximal atoms cannot be equivalent unless they belong to superposable *f*-ligands. Until recently this condition might have been thought to be sufficient, but examples **5**–**7** show that it is not.[2,7d] In **6a**, *e.g.*, by severing all bonds to the central carbon we obtain as the *f*-ligands H and three ligands composed of the outer circle with the proximal atoms A_1, A_2, and A_3. These three ring *f*-ligands can be superposed by a rotation through $2\pi/3$ or $4\pi/3$. There is, therefore, no difference between these ligands, but we can discern one between the proximal atoms. In going from A_1 to A_2 through the peripheral bonds we first traverse a double bond, whereas we cross a single bond first if we go to A_3. A_3 and A_2 are therefore not equivalent as they differ in their connectedness to A_1. We have analogous differences in connectedness between the pairs A_1 and A_3 to A_2, and A_2 and A_1 to A_3, and conclude that all three proximal atoms are not equivalent. As a result of this difference we can connect the central atom with A_2 and A_3 in the two nonequivalent ways shown in **6a** and **6b**. In **5a** we have two pairs of superposable *f*-ligands with the proximal atoms A_1, A_2, and B_1 and B_2. We could not have the two isomeric forms **5a** and **5b** if the two A atoms (or B atoms) were equivalent. They are not because, *e.g.*, A_1 but not A_2 is linked to B_1 through an amide bridge. Finally in **7a** we have four superposable *f*-ligands with four nonequivalent proximal atoms because A_1 is differently connected to A_2 and A_4 and unconnected (except through the central carbon or the two other proximal atoms) to A_3. In **5** and **6** at least one *f*-ligand is different from the others, but in case **7** we cannot say that isomer **7d** can be produced from **7a** by an exchange of *f*-ligands because they are indistinguishable. However, in this case as in all others we can attribute the difference between isomers to an exchange of nonequivalent proximal atoms. (**7b** gives **7c** by an exchange of A_3 and A_4.) Definition [1c] accommodates this unusual case. To define these concepts:

[3] **Assemblies of Differentiated Atoms.**—An assembly[17] of differentiated atoms at a center consists of the ligating atom and those directly linked to it. These atoms occupy the same positions they do in the molecular model (except for the customary adjustment of minor inequalities in bond lengths and bond angles). Any two of the proximal atoms are either *equivalent* or *distinct*. They are equivalent only if (1) they belong to superposable *f*-ligands [2], and (2) if their bonding relationships to any other individual proximal atom of the same center are the same.

This differentiation of proximal atoms wil be indicated in the formulas by capital letters. They will receive different letters (A, B, C, ...) if their difference is due to a difference in ligands, and the same capital letter with different subscripts (A_1, A_2, ...) if they differ only in connectedness to another proximal atom.

If we disregard the fact that some potential stereoisomers may be too strained to be realized, we can replace the molecular model by the assembly of differentiated atoms and find that *a ligating atom is at a center of stereoisomerism if and only if these differentiated points can exist in two or more nonsuperposable distributions*. It is easily verified that none of the alternative definitions of ligands that have been proposed would have given a differentiation of the proximal atoms that would have allowed this generalization.

2. Chiral and Achiral Centers of Stereoisomerism.—In examining a fully defined object, such as a molecular model, one can test whether it can or cannot be superposed on its mirror image and therefore state, without ambiguity, whether it is achiral or chiral.[10] If one subjects a center of stereoisomerism to such a reflection test, one can conduct the test in two distinct ways which reveal different properties of the center. We are presenting both before proposing a definition of the chiral center.

One may wish to determine whether the configura-

(17) The "reference assembly of point ligands" employed previously[3] in defining prochiral centers and the "assembly of differentiated atoms" discussed here are based on essentially the same concept. In both cases the individual ligands are replaced by points that are either equivalent or distinct and that occupy defined positions in three-dimensional space. The two approaches differ in the way the equivalence or difference of these points is established and in the conclusions that are drawn from this form of examination. For example, a center was previously held to be chiral if the assembly of point ligands was chiral, whereas the chirality of an assembly of differentiated atoms is now used as an index of a chiral configuration [4]. We are including the ligating center in the assembly of differentiated atoms to accommodate cases where the proximal atoms are at the base and the center at the vertex of a pyramid.

tion of a center of stereoisomerism, viewed apart from that of any other center of stereoisomerism of the same molecule, can be described only by reference to a chiral object with a defined sense of chirality. Such a chiral descriptor is needed if the assembly of differentiated atoms [3] cannot be superposed on its mirror image. If it cannot be superposed, two enantiomeric configurations are possible and these, obviously, can be distinguished only by chiral descriptors. Therefore, by subjecting the assembly of differentiated atoms to a reflection test we determine a fundamental property of the center which can be expressed as follows:

[4] **Chiral and Achiral Configurations.**—A center of stereoisomerism [1c] has a chiral configuration if its assembly of the differentiated atoms [3] cannot be superposed on its mirror image. If superposition is possible the assembly and therefore the configuration is achiral.

If we apply this to the central carbon atoms of the enantiomers of glyceraldehyde, of the optically inactive diastereomers of the trihydroxyglutaric acids (example of **1**), or to the carbinol carbon atoms of 1,4-cyclohexanediol (**4**), we find that all these have chiral configurations.[18]

Ebel[19] did not regard the carbon atom shown in **1** as asymmetric because it can "keine selbständige optische Aktivität hervorrufen." This indicates a different concept because it seems to imply that an asymmetric carbon atom is one that can contribute to the chirality of the structure. Such a contribution can be revealed by a second type of reflection test that would reflect the whole molecular model. As a chiral structure is being reflected into its enantiomer, any element of stereoisomerism that contributes to the chirality of the whole would undergo a change in configuration. If we adopt this as our test for a chiral center, we need a fixed and incontestable procedure for determining whether the configuration is retained or not. We face no choice if the set of ligands attached to the center remains unchanged on reflection of the model. This is the case in examples **1** and **3**. We can superpose the assemblies of differentiated atoms derived from the original (**1a**, **3a**) and from the reflected model (**1b**, **3b**) in case **1** but not in **3**. Therefore, the configuration of the central atom of **1** but not of **3** is retained on reflection of the whole structure. As example **2** shows, the set of ligands need not remain unaltered by the reflection and we shall have to decide whether the h^- or i^+ ligand of the reflected set corresponds to the h^+ of the original one. The proper procedure can be deduced from the case $Cg^+g^-hi^+$ which on reflection changes to $Cg^-g^+hi^-$. As the three ligands which are common to both sets fully determine the configuration, it follows that the fourth ligand of the original set (i^+) corresponds to the i^- ligand of the reflected set. As a reflection of the model can only invert a ligand or leave it unchanged, no other alternative will ever have to be faced. Consistency demands that we adopt the following rule in order that the configurations of a center of stereoisomerism may be compared before and after the reflection of a molecular model [6].

[5] **Corresponding Proximal Atoms.**—Proximal atoms at a center in an original and a reflected model correspond if the *f*-ligands [2] that contain them are superposable. If there remain proximal atoms that cannot be paired according to this rule, a proximal atom in the reflected model corresponds to that proximal atom in the original model that is associated with an enantiomeric *f*-ligand.[20] If proximal atoms in the original model are differentiated only by different bonding relationships to another proximal atom of the same center, these relationships must be preserved when choosing the corresponding proximal atoms in the reflected model.

Case **2** serves to illustrate the first part of this rule. Ligands g^+ and g^- are common to both the original (**2a**) and the reflected (**2b**) model. This determines the location of the proximal atoms that are labeled A and B. The remaining two ligands, h^+ and i^-, are found only in **2a**. According to [5] the proximal atoms of h^+ and h^- correspond and were, therefore, given the same designation (C). Similarly the corresponding proximal atoms of i^- and i^+ are designated D. As the two assemblies can be superposed, the configuration of the central atom of **2** is retained. According to the criterion under consideration, this center is achiral although the compound is not. Its chirality is due to the uncompensated chirality of the steric elements of the h^+ and i^- ligands.

The second part of [5] was justified when the stereoisomerism of examples **5**–**7** was discussed. In applying it we find that the selection of A_1 in the reflected models of **5**–**7** allows a choice which, however, has no effect on the outcome of the superposition test because the proximal atoms labeled with the same letter are homotopic.[13a] Once this choice has been exercised, the locations of the remaining proximal atoms (B_1, A_2, B_2 in **5**; A_2, A_3 in **6**; or A_2, A_3, A_4 in **7**) are unambiguously determined by their bonding relationships. The assemblies of the corresponding atoms derived from the original and reflected models of these compounds are enantiomeric and the central atoms are, therefore, chiral centers of stereoisomerism according to both criteria. No other conclusion would be acceptable, as the only element of realizable stereoisomerism present in these compounds is the center, which is, therefore, the only element which can be held to be responsible for the chirality of the whole.

If a center of stereoisomerism is directly ligated to three atoms or tetrahedrally to four, only two configurations are possible, and if a reflection causes a change of configuration it necessarily changes it to the enantiomeric one. As these enantiomeric configurations can be distinguished only by chiral descriptors it follows that such a center meets both criteria that we have con-

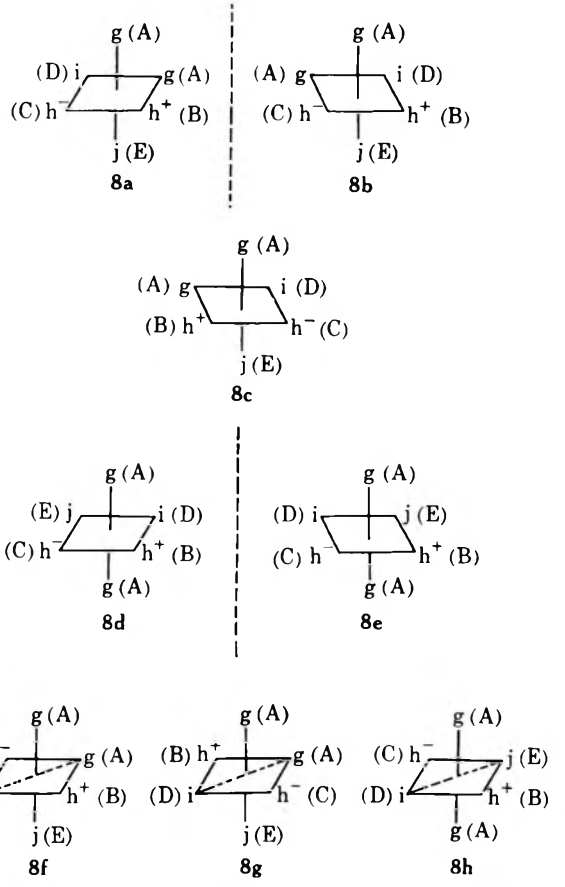
(18) Of these, only the configurations of the glyceraldehydes and of the pentaric acids are specified by chiral descriptors (*R*/*S* or *r*/*s*, respectively) under the rules of Cahn, *et al.*[2] Although it would be quite simple to design a system that would allow one to describe also the configurations of C-1 and C-4 of **4** by relating each individually to an external chiral reference standard, there is no incentive to do this because we can combine both carbinol carbons into a single steric unit and call the isomers cis and trans. This form of analysis is discussed further in section B.4.

(19) F. Ebel in "Stereochemie," K. Freudenberg, Ed., F. Deuticke, Leipzig, 1933, p 599.

(20) This rule is unambiguous if the center is tetrahedral but may require a supplementary statement in other cases. An example (**24**) will be discussed at the end of section A.4.

sidered for a chiral center: the configuration is chiral and it changes on reflection of the model.

However, if the four proximal atoms occupy the corners of a tetragon or if more than four atoms are directly ligated to a center, permutation of their distribution about the center allows more than two nonequivalent configurations. In such a case a reflection of the molecular model may change the configuration to one that is the *diastereomer* of the original one. This is illustrated by example **8** which shows eight of the 15 stereoisomers of the octahedral center Xggh$^+$h$^-$ij. In any one of the isomers **8a–e**, the configuration, as defined by



(-----) mirror plane or intersection of mirror plane with plane shown in formula

the assembly of corresponding atoms and indexed by capital letters, is changed upon reflection of the model to a diastereomeric one. The configuration[21] itself may be chiral, as in **8a–c** (the reflection of **8a** gives the enantiomer **8b** with a diastereomeric configuration, whereas **8c** is the diastereomer that has the configuration enantiomeric to that of **8a**), or achiral, as in the pair of enantiomers **8d** and **e**. All these isomers are themselves chiral and we must acknowledge that their chirality depends upon the configuration of the central atom because we can obtain achiral isomers (**8f–h**) by a different spatial distribution of the same ligands. This supports our contention that a center that undergoes any change in configuration on reflection of the model can contribute to the chirality of the whole—it is not necessary that the change is to an enantiomeric configuration. The configuration of the central atoms of the achiral isomers (*e.g.*, **8f–h**) is retained on reflection of the model. Again the configuration[21] of the centers may be chiral, as in **8f** and **g**, or achiral (**8h**). The relationship between **8f** and **g** is analogous to the diastereoisomerism that results from a change of configuration of the so-called pseudoasymmetric carbon atom of **1**.

We have thus observed all four categories that can result from applying the two reflection tests: centers of stereoisomerism either do or do not change configuration on reflection of the molecular model and each of these types has either a chiral or an achiral configuration. The criteria which determine these properties were formulated without an arbitrary choice, but we are unable to deduce from basic principles whether one ought to call a center chiral if it changes configuration on reflection of the model (*i.e.*, can contribute to the chirality of the whole), or if its configuration is chiral (*i.e.*, requires a chiral descriptor), or if it meets both criteria. A choice might be based on greater utility or on tradition. Although utility would suggest otherwise, tradition has set up the central carbon of glyceraldehyde as the paradigm of an asymmetric center and distinguished such atoms from pseudoasymmetric atoms of type **1**. This view was upheld by Cahn, *et al.*[2], who called only the former centers chiral. As the chiral center of glyceraldehyde meets both criteria for chirality, we merely continue this tradition if we suggest that both be used for the general definition of a chiral center. To formalize:

[6] **Chiral and Achiral Centers of Stereoisomerism.** —A center of stereoisomerism is chiral if (1) it has a chiral configuration [4] and (2) the configuration changes on reflection of the molecular model; it is achiral if it fails to meet either test. The configuration changes if the assembly of differentiated atoms [3] cannot be superposed on the assembly of corresponding atoms [5] derived from the reflected model.

According to these definitions isomers **8a–c** have chiral and **8d–h** have achiral centers of stereoisomerism. The configurations of **8a–c** and **8f,g** are chiral, those of **8d,e,h** are achiral. As we have seen, the type of nomenclature required depends more on the character of the configuration than on the classification of the center itself. It will be useful, therefore, to consider configurations as well and to subdivide the class of achiral centers of stereoisomerism. One category [7] is a traditional one, another [11] will be described in the next section.

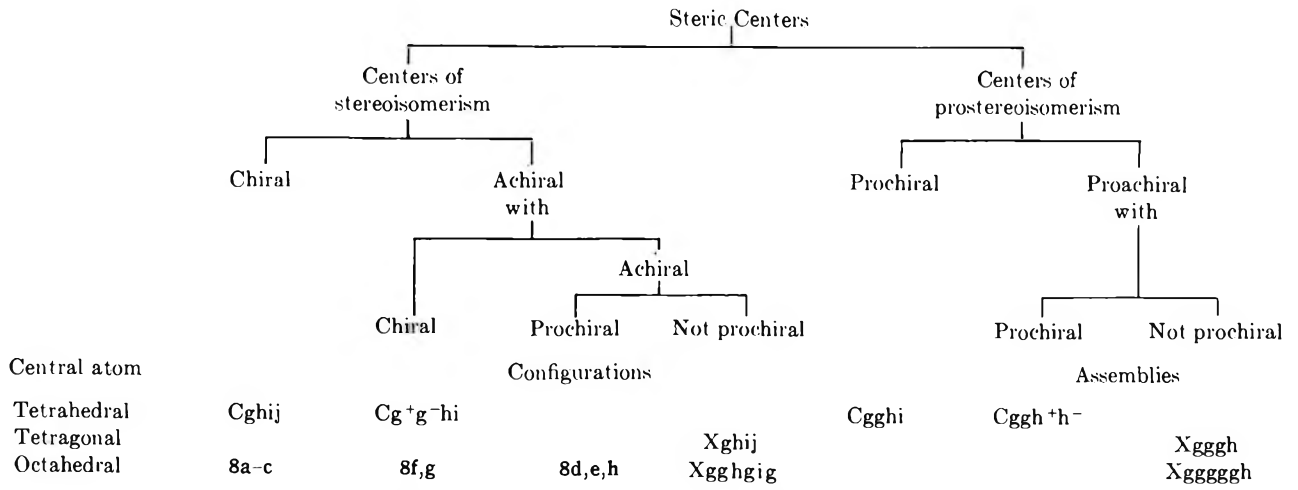
[7] Atoms that are being termed pseudoasymmetric can be defined as atoms at achiral centers of stereoisomerism [6] that have chiral configurations [4].[23]

(21) The descriptions of the configuration of **8a–c,f,g** must include an index with a defined sense of chirality. Such an index is provided by the octahedral chirality rule[2,22] and serves as the sole distinguishing mark for the pairs **8a,c** and **8f,g**. It is neither necessary nor possible to use a chiral descriptor for specifying the configuration of the centers with achiral configurations (**8d,e,h**). Of course, we need to know what is meant by h$^+$ and h$^-$, but this is clearly a separate question. We can distinguish between the enantiomers **8d** and **8e** by stating which h ligand is opposite to i or j, either directly or by means of the numbering system advocated by Cahn, *et al.*[2]

(22) The problem of ascertaining without an arbitrary convention whether two stereoisomers at an octahedral chiral center have the same or inverted sense of chirality has been discussed by E. Ruch, *Theor. Chim. Acta*, **11**, 183 (1968); also E. Ruch and A. Schönhofer, *ibid.*, **19**, 225 (1970).

(23) Cahn, *et al.*,[2] have noted that the configurational symbols for pseudoasymmetry (*r* and *s*) are unchanged on reflection of the model. This observation would be in keeping with our definition but cannot be used as a definition in its place because exceptions to their rule exist (*e.g.*, C-2 of **22**). Moreover, under the sequence rule some chiral centers also retain their configurational symbols on reflection. Such a case (C-1 of **22**) is discussed in section A.4 (examples).

CHART I[a]



[a] No entry means that no example is possible for the type of central atom and class of steric center under consideration.

3. Centers of Prostereoisomerism and Prochirality.—As we have discussed elsewhere,[13b] there exist superposable *f*-ligands of the same central atom that can be differentiated from each other by suitable chemical or physical probes. A common example is provided by the ligands designated g in Cgghi. These ligands have been termed stereoheterotopic,[13a] as they reside in sterically distinct environments, and the center to which they are attached has been said to be prochiral[3] because the center is achiral but would become chiral if one of the g ligands was held to differ from the other and from h and i. One often has need to distinguish such ligands in nomenclature and, in the example given, can obtain the required pair of distinctive descriptors by determining whether the center would acquire the *R* or *S* configuration if one of these ligands (g) were given sequence rule priority over the other.[3] Such a center is not a center of stereoisomerism. Therefore, in general, if we wish to carry out a complete steric description of compounds and their constituent parts we will need to identify some sterically relevant centers that are not centers of stereoisomerism. We wish to call examples of this second type of steric center centers of prostereoisomerism and to classify them by relating them to centers of stereoisomerism as follows:

[8] **Centers of Prostereoisomerism.**—An atom is at a center of prostereoisomerism if it is not at a center of stereoisomerism [1c] and if it is linked to two superposable *f*-ligands [2] that are so located that the center would be a center of stereoisomerism if one member of this pair of superposable *f*-ligands were considered to be wholly different from all others at that center; *i.e.*, it is neither superposable upon nor enantiomeric to any other *f*-ligand.

[9] **Prochiral and Proachiral Centers of Prostereoisomerism.**—A center of prostereoisomerism [8] is prochiral or proachiral, respectively, if the center that results from the change [8] of one of the superposable *f*-ligands is chiral or achiral [6].

One can determine the chiral or achiral character of the stereoisomerism that would result if one or the other of the superposable *f*-ligands underwent the same change [8], if one examines the assembly of differentiated atoms (*cf.* [4]).

[10] **Prochiral Assemblies.**—An assembly of differentiated atoms at a center [3] is prochiral if it is superposable upon its mirror image (*i.e.*, is achiral) and if it contains two equivalent proximal atoms [3] so located that it would become chiral if either member of the pair were considered to differ from all others in the assembly.

If the assembly is prochiral, a chiral terminology is required for differentiation between the *f*-ligands associated with such a pair of equivalent proximal atoms. As a chiral center always has a chiral assembly [6], a prochiral center (which would change to a chiral one on substitution [9]) must have a prochiral assembly. If the center is proachiral the assembly may or may not be prochiral.[24] Simple examples of these categories will be shown in Chart I.

If two superposable *f*-ligands are stereoheterotopic[13a] and attached to a tetrahedral center, this center is necessarily a center of prostereoisomerism. However, if the center is tetragonal or bonded to more than four proximal atoms, the two superposable *f*-ligands can also be found at centers of stereoisomerism. Example **8** gives an illustration of this, because the centers were shown to be centers of stereoisomerism and because the two *f*-ligands designated as g are stereoheterotopic as they cannot be superposed by an operation of gyrosymmetry.[13a] If we fully specify the chiral configurations of isomers **8a–c,f,g** (*e.g.*, by the combination of numbering and a chiral descriptor assigned by the octahedral chirality rule, as advocated by Cahn, *et al.*[2]), we have also specified the position of every ligand in these molecules and can refer individually to either one of the pair of the superposable ligands. This approach will not distinguish the positions of the superposable *f*-ligands in the isomers with achiral configurations (**8d,e,h**). We note, however, that their configurations would become chiral if one of the equivalent proximal

(24) In the system proposed by Hanson[3] different chiral descriptors are used in the two cases. Superposable *f*-ligands at a prochiral center are distinguished by the terms *pro-R* and *pro-S*, whereas *pro-r* and *pro-s* are used if the center is proachiral [9] and the assembly of differentiated atoms is prochiral [10].

atoms were considered to be different from any other. We could therefore characterize the position of this altered proximal atom and its associated *f*-ligand by specifying the sense of chirality (*e.g.*, *R* or *S*) that would result from the change. It is useful therefore to delineate a further subclass of an achiral center of stereoisomerism as follows:

[11] An achiral center of stereoisomerism [6] has a *prochiral configuration* if it has a prochiral assembly [10].

Achiral centers of stereoisomerism with prochiral configurations can occur only if at least five *f*-ligands are joined to the center.[25]

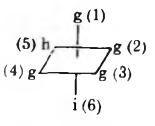
4. Examples.—The full classification presented in the above sections is summarized in Chart I. All criteria used to delineate the various categories were given above ([1c]–[11]); illustrations are shown in Chart I and Tables I and II.

It seems desirable to shorten the names of the four main classes; the chiral and achiral centers of stereoisomerism and the prochiral and proachiral centers of prostereoisomerism. We shall speak instead of chiral, achiral, prochiral, and proachiral centers with the understanding that the term center, if used in this context, always refers to a steric center, *i.e.*, a center which is either a center of stereoisomerism or of prostereoisomerism.

We are not suggesting at this time concise terms for the various subclasses shown in Chart I. The full classification of a steric center according to our criteria will rarely be required as it will usually suffice to indicate the relevant property (*e.g.*, a center with a chiral or with a prochiral configuration).

According to the exchange test [1c] examples **9**, **10**, and **1**–**3** are centers of stereoisomerism. All have four distinct *f*-ligands and therefore chiral configurations. These configurations are inverted on reflection of **9**, **10**, and **3** but not of **1** and **2**. Only the former group, therefore, has chiral centers. Examples **11**–**13** are not centers of stereoisomerism but of prostereoisomerism. On replacing one of the pair of superposable ligands by a new ligand (h), example **11** would change to **9** and is, therefore, prochiral. Examples **12** and **13** are proachiral centers as they would change to **1**.

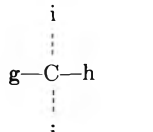
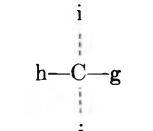
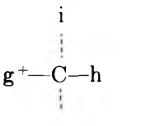
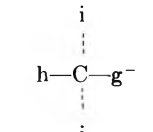
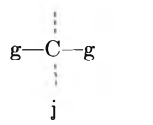
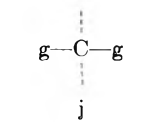
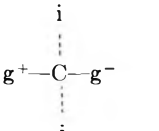
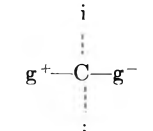
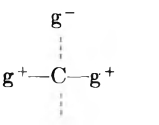
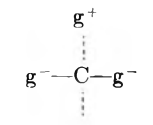
(25) An achiral center with a prochiral configuration [11] may have more than two superposable *f*-ligands. In testing [10] whether a chiral assembly results if one of these *f*-ligands is altered we must not pick this ligand at random. In the following example a replacement of a g by j would not result in a chiral assembly of proximal atoms if the change were made at positions 1 or 3, but it would at 2 or 4.



The proximal atoms at 2 and 4 lie across the plane of symmetry of the assembly and can receive alternative numbering under the rules proposed by Cahn, *et al.*[2] (assumed priority order g > h > i). No specific suggestions have been made for the distinction in nomenclature of stereoheterotopic[13a] superposable *f*-ligands at octahedral centers. We think it most convenient to distinguish their position by numbers using as far as possible the above rules.[2] If these rules leave a choice between two alternatives, the one is chosen that would result in the *R* (or *r*) configuration if at the first point of difference the ligand with the lower number had sequence-rule priority over the superposable *f*-ligands with the higher numbers. The symbols *R*-n for *R*-numbered, or *r*-n for *r*-numbered, would be used to indicate that this subsidiary rule has been applied. In the above example *R*-numbering is shown, as the configuration would be *R* if the *f*-ligand numbered 2 had priority over those at 3 and 4. In **8d**,**e**,**h** position 1 is on top if **8d** and **8e** are *R*-n and **8h** is *r*-n and the priority sequence is g > h$^+$ > h$^-$ > i > j.

TABLE I

STERIC CENTERS WITH UNIDENTATE LIGANDS[a]

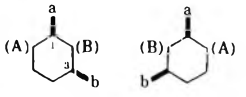
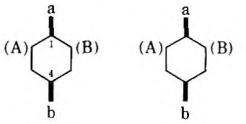
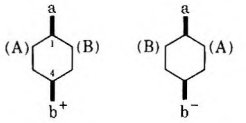
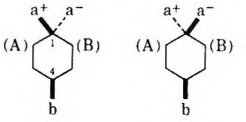
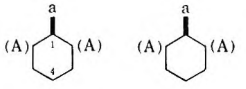
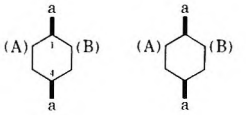
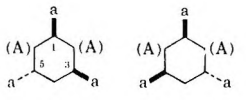
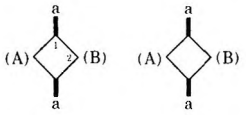
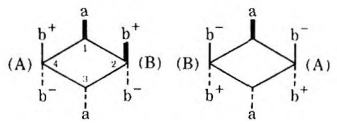
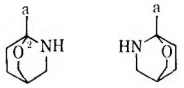
	Model (object, *O*)	Reflection (image, *I*)	Assignment of center
9			Chiral
10			Chiral
1	See text		Achiral[b]
2	See text		Achiral[b]
3	See text		Chiral
11			Prochiral
12			Proachiral[c]
13			Proachiral[c]

[a] See footnote 5. [b] This achiral center (of stereoisomerism) has a chiral configuration [4]. [c] This proachiral center (of prostereoisomerism) has a prochiral assembly [10].

The carbon atom numbered C-1 of **20** is not at a center of stereoisomerism because an exchange of its ligands H and a does not produce a stereoisomer. Its two other *f*-ligands which constitute the ring can be superposed with their proximal atoms coinciding. Both C-2 and C-6 are therefore equivalent proximal atoms of C-1 and receive the same designation (A). As C-1 would be a chiral center if these ring ligands were distinct (as those of C-1 in **14**), this center is classed as a prochiral center. In contrast, C-5 of **20** is a center of stereoisomerism because an exchange of *f*-ligands would yield the all-cis isomer. Its ring *f*-ligands are enantiomeric. If we reflect the molecular model in a plane perpendicular to the ring through C-2 and C-5, the corresponding proximal atoms of C-5 keep their positions. This shows that the configuration of C-5 is retained on reflection of the model and that C-5 is at an achiral center. The same classification applies to any center of stereoisomerism that lies in a plane of symmetry of the molecule.

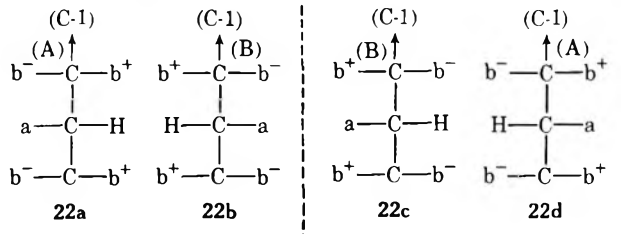
Example **22** is of interest because C-1 and C-3, which lie across a center of symmetry, receive in the *R*/*S* system the same configurational symbols which therefore do not change upon reflection. Nevertheless, analysis shows that these are chiral centers of stereoisomerism. As the two ring *f*-ligands of C-1 in **22**-(*O*) are distinct (**22a**,**b**), their proximal atoms are nonequivalent. On reflection of the model these *f*-

TABLE II
STERIC CENTERS WITH PLURIDENTATE LIGANDS[a]

	Model (object, *O*)	Reflection (image, *I*)	Assignment of center	
14			C-1 C-3	Chiral Chiral
15			C-1 C-4	Achiral[b] Achiral[b]
16			C-1 C-4	Chiral Achiral[b]
17			C-1 C-4	Chiral Chiral
18			C-1 C-4	Prochiral Proachiral[c]
19			C-1 C-4	Achiral[b] Achiral[b]
20			C-1 C-2 C-3 C-4 C-5	Prochiral Proachiral[c] Prochiral Prochiral Achiral[b]
21			C-1 C-2	Achiral[b] Proachiral[c]
22			C-1 C-2	Chiral Achiral[b]
5–7	See text		Central C	Chiral
23			C-2	Chiral

[a] The markings (A, B) of the proximal atoms refer to C-1; see footnote 5. [b] This achiral center (of stereoisomerism) has a chiral configuration [4]. [c] This proachiral center (of prostereoisomerism) has a prochiral assembly [10].

ligands change to **22c,d** which cannot be superposed on the original pair. In this case [5] the enantiomeric pairs, **22a,d**, and **22b,c** correspond. The corresponding proximal atoms (A and B) of the reflected model 22-(*I*) are therefore located as shown. It is evident that



22a **22b** **22c** **22d**

ligands of 22-(*O*) ligands of 22-(*I*)
(--- mirror plane)

the two assemblies of differentiated atoms cannot be superposed and that the center is chiral.

In this as in the other examples shown in these tables, the pairing of the proximal atoms of chiral ligands before and after reflection is unambiguously defined by the criterion given [5]. This need not be true if the center is tetragonal or octahedral rather than tetrahedral. Example **24** illustrates such a case. The central atom of **24**-(*O*) is a center of stereoisomerism which changes to **24**-(*I*) on reflection. We can pair the h and g^- and one of the g^+ ligands of **24**-(*O*) with superposable ligands of **24**-(*I*), but we must make a choice as to which of the two g^+ ligands of **24**-(*O*) is thought to be paired with the sole g^+ of **24**-(*I*). As we always conduct the superposition test between a model containing two achiral superposable *f*-ligands and its mirror image in such a way that superposition of the corresponding proximal atoms results if this is possible, we regard it as consistent if we exercise the option in pairing proximal atoms in such a way that whenever possible superposition of their assemblies can be achieved. Superposition is possible if the g^+ ligand adjacent to h in **24**-(*O*) is paired with the one in **24**-(*I*), which means that the g ligands diagonal to h in **24**-(*O*) and **24**-(*I*) are the ones that are not common to the two structures and which consequently are to be paired as enantiomers. This pairing is presented with **24** and shows that the two assemblies (XAABC) can be superposed by a rotation of a diagonal axis through the proximal atom C. The center of **24** is therefore achiral. As the plane of the tetragon is a symmetry plane of the assembly of differentiated atoms, the configuration is likewise achiral; the compound, of course, is not.

24-(*O*) **24**-(*I*)

Cahn, *et al.*,[2] have given numerous examples of chiral and of achiral octahedral centers of stereoisomerism. All would receive the appropriate classification under the definitions which we have presented.

B. Other Elements and Units of Stereoisomerism and of Prostereoisomerism

It follows from [1b] that the stereoisomers resulting from an exchange of *f*-ligands at an improper center of stereoisomerism have superposable assemblies of differentiated atoms for the center. These stereoisomers usually contain a second improper center such that the two isomers are also interconverted by an exchange of *f*-ligands at this center. By constructing an assembly containing both centers and their proximal atoms one can obtain a larger entity that differs for the two isomers. This allows their distinction and represents an *element of stereoisomerism*[26] if, in case of a choice, the two improper centers are as close as possible. The isomerism of the olefins provides a simple example. The olefinic carbons are the improper centers of stereoisomerism which singly do not permit a descrip-

(26) An element of stereoisomerism may be defined as a structural type equivalent to the most compact assembly that permits stereoisomerism by a different spatial distribution of differentiated proximal atoms.

tion of configuration. The element of isomerism consists of the two atoms linked by the double bond and the differentiated proximal atoms singly bonded to these centers.

Occasionally a structure contains two proper centers of stereoisomerism [1c] that are so interrelated that a change of configuration at either center produces the same isomer and a change at both restores the original structure. In many such cases it is convenient to describe a larger entity that combines the individual centers and their proximal atoms into a steric unit as this will permit the use of a single descriptor of configuration. The cis–trans isomerism of the 1,4-disubstituted cyclohexanes has long been recognized as such a case. Although geometrically related to the cis–trans isomerism of the olefins, the two cases differ in that an entity that can be resolved into elements of the same stereoisomerism is not, strictly speaking, an element and is more suitably termed a unit. Such *units of stereoisomerism* may contain elements besides proper centers.

Among the larger entities that contain general centers of stereoisomerism [1a] the axis and plane of stereoisomerism became important when Cahn, *et al.*,[2] showed that the chirality of many structures that had been classed as having only "molecular asymmetry" could be attributed to chirality with respect to a line (axis) or a plane. These latter two concepts are not necessarily mutually exclusive, as the same partial structure can often be viewed as either a chiral axis or a chiral plane.

1. Axes of Stereoisomerism and of Prostereoisomerism.—Cahn, *et al.*,[2] derived axial chirality and axial pseudoasymmetry by giving one dimension to the corresponding tetrahedral centers. They observed such axial chirality among the chiral allenes, alkylidenecycloalkanes, spirans, biaryls, and adamantoids, but excluded some chiral spirans although the four ligands occupied the four corners of an elongated tetrahedron. One of these is **25**, which was excluded because C-4 is a chiral center; others are spirans of type **5** where the axis which may be thought to be desymmetrized by the C=O and NH groups is occupied by only one atom, the chiral carbon at the center. It seems that the chiral axis and related achiral structures can be defined by an approach closely analogous to the one used in defining and classifying steric centers and in a manner that would exclude such cases as **5** and **25**. The axis of chirality was introduced as a geometric concept and illustrated by examples[2] that we would classify as either elements (*e.g.*, allenes) or units (*e.g.*, alkylidenecycloalkanes) of axial stereoisomerism. We have therefore phrased our definition to cover both types.

[12] **Axes of Stereoisomerism.**—An axis of stereoisomerism is a structure that contains two general centers of stereoisomerism [1a] (1) so interrelated that an exchange of differentiated proximal atoms [3] at either center produces the same stereoisomer and an exchange at both restores the original structure and (2) so oriented that the planes defined by the centers and the proximal atoms specified in [13] intersect at a large angle (usually 90°). The general centers, which should be as close to each other as possible, may be either trigonal or tetrahedral and an unused bonding orbital may be treated as a proximal atom for the purposes of the above tests. The straight line between two such centers of stereoisomerism is termed an axis of stereoisomerism with the two centers as its *terminal atoms*. These atoms, the bond(s), and any other atoms that connect them by the shortest path we term the *core*, and, if there are two or more alternative paths of equal length, no distinction is made between them but all are included in the core.

Cores analogous to the ones described for the axis of stereoisomerism will be defined below (B.2–4) for other steric elements and units. Definitions [13]–[17] have been so phrased that they are applicable to any of these elements and units. In these we shall, for the sake of brevity, speak of the steric character of a core in the same general sense as one customarily speaks of the chirality or configuration of an atom or center. The correspondence between these definitions and the definitions for a steric center will be apparent: [13] to [2], [14] to [4] and [3], [15] to [6] and [5], [16] to [8] and [9], and [17] to [10].

[13] **Core-Factorization Ligands.**—The *cf*-ligands of a core are the structures that result from separating from the core that part of the molecule that is bonded to the terminal atoms. A *proximal atom* of a core is part of a *cf*-ligand and is directly attached to a terminus. A ligand joined to terminal atoms in n bonds is treated as n separate factorization ligands each with its proximal atom as described [2].

[14] **Cores with Chiral and Achiral Configurations.**—A core of stereoisomerism has a chiral or achiral configuration, respectively, if its assembly of differentiated atoms cannot or can be superposed on its mirror image. The assembly consists of the core and its differentiated proximal atoms. The proximal atoms are differentiated as at the center [3].

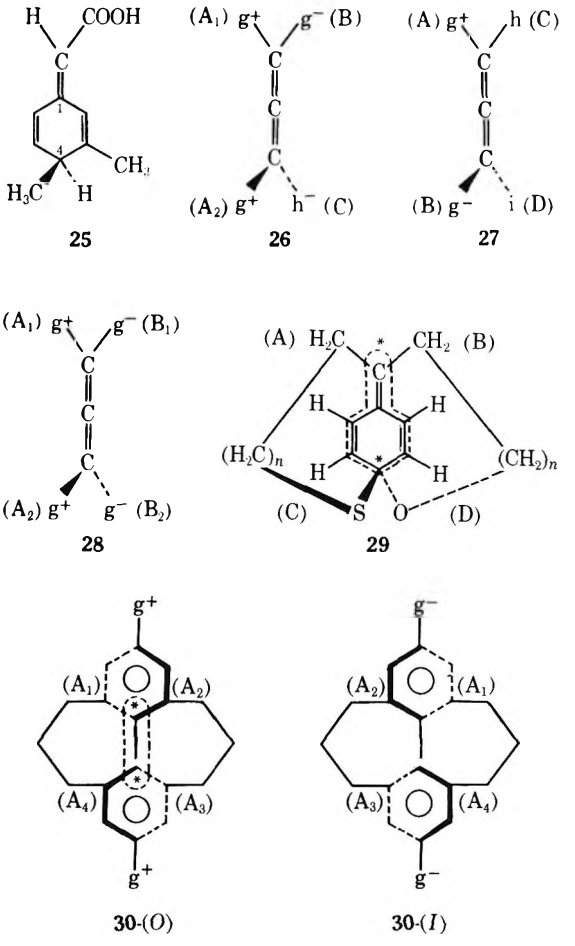
[15] **Chiral and Achiral Cores of Stereoisomerism.**—A core of stereoisomerism is chiral (1) if it has a chiral configuration [14] and (2) if the configuration changes on reflection of the molecular model; it is achiral if it fails to meet either test. The configuration changes if the assembly of differentiated atoms [14] cannot be superposed on the assembly of corresponding atoms derived from the reflected model. Corresponding proximal atoms are determined as described for the center [5]. Again, special bonding relationships must be preserved. These exist if two or more *cf*-ligands are attached to the same terminal atom, if there is bonding between proximal atoms besides that through the core, or if proximal atoms are attached to different terminal atoms that cannot be superposed by an operation of gyrosymmetry[13a] performed on the core. Therefore, whenever such special bonding relationships exist, each terminal atom is examined individually as for the center [5] when the corresponding proximal atoms of the core are determined.

[16] **Prochiral and Proachiral Cores of Prostereoisomerism.**—A core of prostereoisomerism is not a core of stereoisomerism, but would change to such a core if one member of a pair of superposable *cf*-ligands [13] of the core were considered to be wholly different (*cf.* [8]) from all others of the same core. A core of prostereoisomerism is prochiral or proachiral, respectively, if the resulting core is chiral or achiral [15].

[17] **Prochiral Assemblies.**—An assembly of a core [14] is prochiral if it is achiral but would become chiral if one of a pair of equivalent proximal atoms were thought to be different from all others in the assembly.

If one applies these criteria to any axis of stereoisomerism [12], one finds that, as in the case of the tetrahedral center, all have chiral configurations [14], but that the configuration may or may not change to an enantiomeric one upon reflection of the molecular model, *i.e.*, the axis may be chiral or achiral. As would be anticipated from our analysis of centers of stereoisomerism [7], axes that were termed by Cahn, *et al.*,[2] pseudoasymmetric are achiral axes of stereoisomerism [15] with chiral configurations [14]. Axes of prostereoisomerism [16] fail to yield a stereoisomer upon exchange of differentiated proximal atoms at either terminus of the axis; the superposable *cf*-ligands that are held to be different in carrying out the tests for prostereoisomerism and prochirality are attached to the same terminus. As all axes of stereoisomerism have chiral configurations, all axes of prostereoisomerism have prochiral assemblies [17].

Example **26** meets the definitions of an axis of stereoisomerism [12]. Its core consists of the chain of doubly bonded carbon atoms; the terminal atoms are the trigonal carbons at the end of this chain. Both are improper centers of stereoisomerism [1b] that yield the same isomer by exchange; also the bonds connecting the *cf*-ligands g and h to these terminal atoms lie in two perpendicular planes. As the two superposable *cf*-ligands g^+ are in a different bonding relationship to g^- their proximal atoms are distinguished as A_1 and A_2. The distribution of the corresponding proximal atoms does not change if the model of **26** is reflected in the plane g^+Ch^-; therefore the axis is achiral [15], but, as expected, the elongated tetrahedron occupied by the proximal atoms A_1B, A_2C cannot be superposed on its mirror image, *i.e.*, the achiral axis has a chiral configuration. In contrast, **27** and **28** both contain chiral axes of stereoisomerism. These examples show, as do the isomers of **8**, that the description of a pseudoasymmetric carbon atom in the IUPAC rules[10] cannot be applied without revision to steric elements other than the tetrahedral center. Example **25** does not meet the definition of an axis of stereoisomerism [12] as an exchange of the H and CH_3 ligands at C-4 or of the H and COOH ligands at the olefinic carbon does not produce the same stereoisomer. Examples **29** and **30** are somewhat more complex. Their cores are circumscribed by the loops of dashes; their terminal atoms are marked by asterisks. Both are chiral axes of stereoisomerism by the criteria given. For **29** the *cf*-ligands and therefore the differentiated proximal atoms are all nonequivalent. As in examples **26**–**28** and **30**, an exchange of the *cf*-ligands at either terminal yields the same stereoisomer. Its configuration can be completely described either by specifying that of the chiral axis or by stating that of the tetrahedral terminal atom. This is possible for **29**, because this carbon is a proper center of stereoisomerism. It is chiral when tested according to [6]. Because of their bonding relationships the proximal atoms of **30**-(*O*) are nonequivalent although their *cf*-ligands are superposable. They are enantiomers of the *cf*-ligands of **30**-(*I*) which is the mirror image of **30**-(*O*). If one proximal atom (A_1) of **30**-(*O*) is arbitrarily paired with A_1 of **30**-(*I*), the pairing of the remaining three pairs of proximal atoms is uniquely determined by their bonding relationships to A_1. The superposition test [15] shows that the two assemblies are enantiomeric and therefore that **30** has a chiral axis. The case is closely related to one discussed by Mislow, *et al.*,[27] and later by Cahn, *et al.*,[2] but shows in addition that the chirality of an axis can be deduced in such a case by our criterion even when chiral ligands are also present and when, therefore, this deduction cannot be based on the chirality of the whole structure.



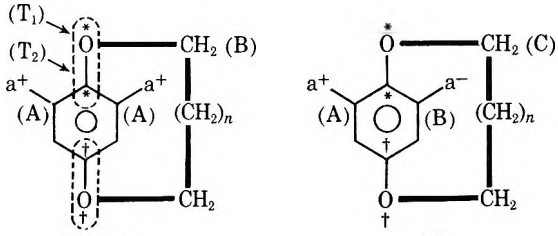
2. **Planes of Stereoisomerism and of Prostereoisomerism.**—In the plane, as in the axis of stereoisomerism, a core structure with two terminal atoms can

(27) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, Jr., *J. Amer. Chem. Soc.*, **86**, 1710 (1964).

be identified.[28] One of these (T_1) is an atom that lies in the plane and is directly joined to an out-of-plane group that is limited in its orientation to one side of the plane. The second terminal atom (T_2) is the nearest improper center of stereoisomerism [1b] that is linked to the first by bonds lying in the plane and so related to T_1 that the same stereoisomer can be produced by a change of orientation of the out-of-plane group from one side of the plane to the other or by an exchange of differentiated proximal atoms [3] at T_2. If both of these changes are made the original structure is restored. The core consists of these two terminal atoms together with the bond(s) and any atoms that connect them by the shortest path. In applying [13]–[17] one finds that, as for the axis, all planes of stereoisomerism have chiral configurations [14] and all planes of prostereoisomerism [16] have prochiral assemblies [17]. Although proachiral planes can be conceived, it appears that such structures can alternatively be factorized into proachiral axes.

If the out-of-plane group that induces stereoisomerism is a simple bridge, as is generally the case, two cores usually can be identified that are interrelated in the sense that the plane has the same basic character relative to each core, *i.e.*, it is either a chiral or an achiral plane of stereoisomerism or a plane of prostereoisomerism. The latter is illustrated by example **31**. The two core structures are enclosed by dashes; their two sets of terminal atoms are indicated by the asterisks and by the daggers. The proximal atoms marked A and B refer to the former core. It is evident that the two *cf*-ligands which start at either one of the A's and which end at the other A and at B are superposable. Their exchange would produce a stereoisomer only if they were thought to be different. In this case the core would invert its configuration on reflection. The core, therefore, is prochiral. An analogous examination of the starred core of **32** shows that it is an achiral plane of stereoisomerism with a chiral configuration. The core and its proximal atoms can be superposed on the assembly of corresponding points that result from the reflection of the molecular model, but there is no plane of symmetry through the core and its proximal atoms if all three are distinct. Cahn, *et al.*,[2] have termed such a case a pseudoasymmetric plane. In these cases the ligands at the alternate cores differ constitutionally from the original ones, but this causes no change in the classification of the plane. Example **33** shows a case which, unlike **32**, has two chiral cores, but which resembles **32** in its lack of overall chirality. Example **34**, like **33**, has two chiral cores. As in **33** the *cf*-ligands of one core are the enantiomers of those at the other, but **34** represents a chiral compound. We therefore find that the two cores of a plane of stereoisomerism with such sets of enantiomeric ligands may either compensate (**33**) or not compensate (**34**) each other, and conclude that the elements of chirality are the individual cores and their proximal atoms rather than the larger entity that would result from the combination of two or more such cores.[29] This is, of course, consistent with our definition of an element of stereoisomerism.[26]

The above view is further strengthened by consideration of the examples **35** and **36**. If the planar part



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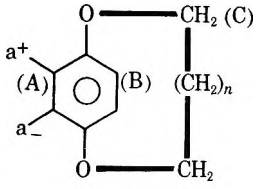

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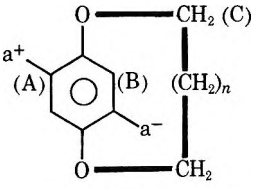

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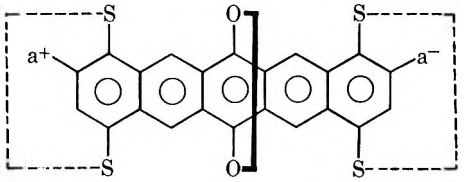

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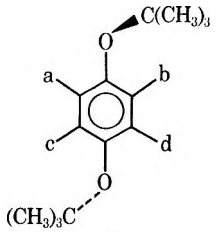

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of the structure is wide enough to allow multiple bridging, the plane can be achiral relative to some of these bridges but chiral relative to others. In **35**, *e.g.*, the two central cores are achiral and the four lateral ones chiral. In most cases studied the out-of-plane group that induces chirality is a single bridge of such span that it cannot swing past the plane to the other side. This fixes the cis relationship of the two out-of-plane proximal atoms of the two cores and thereby ties their configurations. However, one can

(28) The present discussion is limited to structures that maintain their integrity by linking all their parts through at least one bond between *identifiable* atoms. This restriction excludes ferrocenes if these are pictured as having a π bond between the iron and the cyclopentadienyl ring. Such structures can have planes of stereoisomerism which would have to be studied by a core structure different from the one here presented. Alternatively, one can adopt the convention, as Cahn, *et al.*,[2] have done, that there are bonds between Fe and the individual carbon atoms of the cyclopentadienyl ring. From this point of view the elements of chirality present in the chiral ferrocenes are not chiral planes, but chiral centers which fall within the scope of this paper.

(29) In the *R/S* system[2] the choice of the pilot atom on the basis of sequence rule priorities—or an arbitrary choice if the alternative pilot atoms are homotopic[13a]—in effect selects one core as the dominant one. This approach greatly simplifies the specification of the configuration but could lead to complications if, *e.g.*, the plane is chiral relative to two enantiotopic[13] cores (*cf.* **33**). Cahn, *et al.*,[2] have not yet discussed such a case. One might attempt to meet this problem by a rule that a plane should be regarded as pseudoasymmetric if the choice of the pilot atom depends on the priority sequence $R > S$. Unfortunately, this criterion would fail in the closely related case **34** which is chiral while **33** is not. After considering examples **35** and **36**, we see little prospect of evolving a general system (as distinct from a specific nomenclature) that could properly characterize *any* plane by a single term expressing its steric character as the composite of its relationship to all its cores.

conceive planes (*e.g.*, **36**) that still owe their stereoisomerism to restricted torsion (in this case by the bulky *o*-groups, a, b, ...) but that allow the independent variation of the configuration of the two cores. Therefore, the term chiral plane may not only allow but even require further factorization into the individual cores.

3. Torsional Stereoisomerism and Prostereoisomerism.—The existence of two or more nonsuperposable structures that differ only in torsional angles and that do not interconvert readily during the period of observation is a manifestation of torsional stereoisomerism. It can be analyzed for chirality or achirality in analogy to the elements already discussed if the barrier which restricts torsion is considered to be absolute and if conformational changes are allowed only within these limits. As we are usually concerned with differences about a particular bond,[29a] the core consists of the bond about which rotation is restricted and its two terminal atoms. Definitions [13]–[17] may be applied to this core. The three staggered forms of 1,2-dibromoethane, if considered to be fixed, would constitute a well-known example of torsional stereoisomerism. Of these, either one of the two synclinal (gauche) forms is a chiral element and chiral descriptors are needed for their distinction. The antiperiplanar (trans) form is an achiral element of torsional stereoisomerism [15]. It has an achiral configuration and the descriptor is, of course, achiral. These classifications would remain unaltered if the bromine atoms were replaced by chiral ligands such as g^+ and g^+, g^+ and g^-, or g^+ and h^+. Cahn, *et al.*,[2] have provided many other examples of torsional chirality and discussed them in detail. If the rotation around the C–C bond in Chij–Cggg is severely restricted, this bond is an element of torsional prostereoisomerism. A manifestation of such prostereoisomerism was observed during an nmr study of an olefin ijC=Ch[$C(CH_3)_3$], which showed a distinct signal for one of the three methyl groups.[30]

The torsion which produces the stereoisomer should be regarded as a purely conceptual operation. It ought not to be limited to cases where such an event can be realized experimentally any more than we contemplate whether the direct exchange of ligands at a center of stereoisomerism can be an actual phenomenon. In either case the sole criterion of isomerism is the stability of the final product and not the probability of the operation which relates the original structure to its isomer.[31] On this basis alternative forms of analysis are frequently possible. We can thus regard the isomerism of the olefins either as a manifestation of torsional isomerism or as an example of the steric element mentioned before and discussed further in the next section. Similarly, some forms of axial stereoisomerism (allenes, biaryls) and of planar stereoisomerism can be regarded as torsional stereoisomerism. A similar view was expressed by Cahn, *et al.*,[2] who spoke of conformational chirality. According to our presentation the distinction between these alternative forms of analysis is rather unimportant, as the difference lies solely in the operation (torsion or exchange) that is thought to produce the stereoisomer. The actual examination of the isomer, its core, and the *cf*-ligands are the same.

4. Other Steric Elements and Units.—As indicated above, the steric element of the olefins and of other sterically analogous structures can also be regarded as the composite of two improper centers of stereoisomerism [1b]. The core consists of the double bond and of the two double-bonded atoms which are the terminal atoms of the core. Such a double bond regarded as an element of stereoisomerism is always achiral; special comment is indicated only for the type g^+g^-C=Chi, which is a chiral structure. The assemblies of this double bond and its four differentiated proximal atoms derived from the original and the reflected model are diastereomeric. Each individual assembly, however, is achiral and thus the element is classed as achiral in conformity with [15]. Compound *37* of Cahn, *et al.*,[2] is similar to this type and was factorized by them in a manner which seems consistent with this deduction. The situation is analogous to **8d,e** which was discussed in greater detail above.

The cis/trans nomenclature for a 1,4-disubstituted cyclohexane (*e.g.*, **15–17**) treats the two centers of stereoisomerism of such a compound as a unit. Its core would consist of the ring carbon atoms with C-1 and C-4 functioning as the terminal atoms. This unit is achiral in all cases. In **15** and **16** the assemblies of the core and of the corresponding proximal atoms obtained before and after reflection are superposable; in **17** they are diastereomeric, but the individual assembly is achiral. Examples **16** and **17** illustrate, therefore, that the steric character of the unit may differ from that of the individual centers contained therein. Although the unit treatment serves well for the distinction of stereoisomers, full factorization of **15–17** into their centers of stereoisomerism is needed for the naming[13b] of the stereoheterotopic methylene groups that are attached to these centers.

Finally, Cahn, *et al.*,[2] have noted that adamantanes substituted at the four tertiary positions with four different ligands can exist in only two enantiomeric configurations. The four chiral centers can be combined into a single steric unit having as its core the adamantane carbon skeleton and as its terminal atoms the four tertiary carbon atoms. In applying [15] to this unit it should be noted that there are no special bonding relationships between proximal atoms through the core, as all of the termini can be superposed by simple rotations of the core and only one proximal atom is attached to each terminus.

Concluding Remarks

The creation of a universal system for the specification of chiral configurations and conformations by Cahn and his collaborators[2] represented a major advance toward a unique description of chemical structures. If the task of coding for structural infor-

(29a) NOTE ADDED IN PROOF.—This need not be the case if there is a continuous series of collinear bonds as, *e.g.*, in a cummulene. In such a case of torsional stereoisomerism the core would consist of this linear sequence of atoms, while the ends of this chain would constitute the terminal atoms of the core. It seems appropriate, therefore, to refer to any core of torsional isomerism as a *line of torsion*.

(30) A. F. Casy and R. R. Ison, *Tetrahedron*, **25**, 641 (1969).

(31) The probability of a torsional change is, of course, an important question in chemistry, but a distinctive nomenclature is available: *conformational changes* are those changes in the internal coordinates of the nuclei that occur freely during the period of observation and that do not involve changes in bonding; *conformers* are those states of a molecule that differ in conformation and that represent minima of energy (*cf.* ref 10). This definition of conformation is similar to one given by Barton [D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953)].

mation is to be entrusted entirely to machines, they will have to be instructed not only how to examine ligands in order to determine the sense of chirality[2] but also how to decide when such an examination is appropriate and whether, for example, a sinister sense of chirality is to be expressed as *S* or as *s*. These additional problems also call for precise definitions and alone provide sufficient practical justification for an inquiry as to what constitutes a chiral or a prochiral element. We faced no arbitrary choices in formulating relevant criteria and are presenting these tests with the expectation that they can serve their stated objectives. However, we found that an appropriate definition of a chiral element can be based on the outcome of either one or both of two distinct reflection tests. Our decision to use both tests in the definition of a chiral element was prompted by the realization that only this choice provided a classification that would be compatible with the Cahn–Ingold–Prelog system which, in turn, is firmly based on tradition. We present this choice not as the necessarily best solution, but rather as a point of departure for a fuller discussion which might concern itself more with the tasks of the future than with preserving the concepts of the past. Unfortunately we see no *single* answer as to what would be the most useful definition of a chiral element; those who are cataloguing and comparing stereoisomers will have to identify the partial structures that can only be described in chiral terms and these structures are not necessarily the same entities that enter the equations of those who calculate such chiral properties as optical rotation.

In factorizing a structure into the components relevant to the distinction of stereoisomers we have adhered, as far as possible, to the categories set forth by Cahn, *et al.*[2] These classes may allow alternative ways of factorizing a structure. We observed, however, that as long as the assembly of differentiated atoms met our definition of an element of stereoisomerism[26] the use of alternative classifications did not change the nature of either the *f*-ligands or of the framework to which they are attached. Moreover, only two basic types of the elemental assembly are needed to describe all forms of stereoisomerism that we have considered: (1) the assembly of the proper center and (2) the assembly of the line of torsion (B.3). Although the traditional geometric concepts (center, axis, plane, helix,[2] cis–trans isomerism[10]) are serving well as a basis of a comprehensive nomenclature of stereoisomerism, it remains an aim of fundamental stereochemistry to provide a unique mode of factorization for any stereoisomer. The two elemental assemblies of the center and of torsional isomerism appear to meet this objective for any compound that has a fully defined pattern of connectedness[28] between its constituent atoms.

Acknowledgment.—The authors wish to express their indebtedness to all colleagues who commented on drafts of this paper. Particular thanks are due to Dr. R. S. Cahn, who also called our attention to the interesting group of compounds comprised of 22 and its isomers; also to Professors D. Arigoni, A. Dreiding, W. Klyne, K. Mislow, V. Prelog, and H. Z. Sable.

Metal–Ammonia Reduction. XI. Regiospecific and Stereoselective Reduction in the Chrysene Series

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Metal–ammonia reduction of chrysene through the hexahydro stage proceeds regiospecifically *via* 5,6-dihydro- (**1**) and 4b,5,6,12-tetrahydro- (**2**) to 4b,5,6,10b,11,12-hexahydrochrysene (**3**). Existence in liquid ammonia of stable monoanionic intermediates related to **1** and **2**, but not **3**, is demonstrated by reductive methylation. Cis stereoselectivity observed in reduction of both **2** and 5,6,11,12-tetrahydrochrysene to **3** is dependent upon olefin structure. Conformational analysis of **3** indicates three possible conformations of *trans*-**3**, a boat–boat, a boat–chair, and a chair–chair form, and two sets of three similar configurations for *cis*-**3**, a "folded" set and a "twisted" set. The relative importance of thermodynamic, steric, and ion-pair factors in determining product stereochemistry is discussed.

In the previous papers of this series,[1,2] methods for the efficient, controlled reduction of representative polycyclic aromatic hydrocarbons by means of solutions of alkali metals in liquid ammonia were described. These transformations proved uniquely regiospecific (*i.e.*, only a single dihydro isomer formed at each stage), uncomplicated by secondary processes (*e.g.*, isomerization, disproportionation, dimerization, etc.) and frequently also stereospecific;[3–5] moreover, the sites of reduction were in general accord with predictions of molecular orbital theory.[6,7] Analogous reductive alkylations of polycyclic aromatic carbanions in liquid ammonia were found to exhibit similar regiospecificity but generally contrary stereoselectivity.[8–10]

We report now extension of these studies to the chry-

(1) Paper X: R. G. Harvey and P. W. Rabideau, *Tetrahedron Lett.*, 3695 (1970).

(2) *Cf.* review: R. G. Harvey, *Syn.*, 161 (1970).

(3) R. G. Harvey, L. Arzadon, J. Grant, and K. Urberg, *J. Amer. Chem. Soc.*, **91**, 4535 (1969).

(4) P. W. Rabideau, R. G. Harvey, and J. B. Stothers, *Chem. Commun.*, 1005 (1969); P. W. Rabideau and R. G. Harvey, *J. Org. Chem.*, **35**, 25 (1970).

(5) A. W. Brinkmann, M. Gordon, R. G. Harvey, P. W. Rabideau, J. B. Stothers, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **92**, 5912 (1970).

(6) A. Streitwieser, "Molecular-Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 425; A. Streitwieser and S. Suzuki, *Tetrahedron*, **16**, 153 (1961).

(7) Pyrene, however, provided only one of five theoretically predicted equivalent structures.

(8) R. G. Harvey and L. Arzadon, *Tetrahedron*, **25**, 4887 (1969).

(9) R. G. Harvey and C. C. Davis, *J. Org. Chem.*, **34**, 3607 (1969).

(10) P. W. Rabideau and R. G. Harvey, *Tetrahedron Lett.*, 4139 (1970).

sene ring system, in an attempt to further probe the limits of controllability and stereospecificity. Evidence will be presented relating to the nature of the intermediate anionic species, the extent of protonation by the medium, the conformational properties of intermediates, and the relative importance of ion-pair association[10] and other factors in the determination of product stereochemistry. Surprisingly, metal–ammonia reduction of chrysene has not previously been reported[2] and reduction by other means, including catalytic hydrogenation[11] and lithium in ethylenediamine[12] affords highly reduced products, primarily dodecahydrochrysenes.

Results

According to HMO theory,[6] initial reduction of chrysene is expected at the 5,6 bond. Experimentally, reduction of chrysene with lithium in ammonia tended to proceed beyond the dihydro stage to the tetrahydro level. The conditions successfully employed to limit or prevent excessive reduction of other polycyclic hydrocarbons[2] (*i.e.*, low metal–hydrocarbon ratios, rapid quenching with an external proton source, colloidal iron) were relatively ineffectual. A brief investigation (Table I) implicated two factors as primarily responsible: the relative insolubility of chrysene, and the facile protonation of the initial intermediate by ammonia[13] to provide the more soluble and readily reducible 5,6-dihydrochrysene (**1**). These factors were effectively counteracted by use of the most efficient cosolvent (THF > DME > ether), by addition of the metal in portions (method B) rather than all at once (method A), and by use of sodium,[14] rather than lithium or calcium. Yields of **1** under optimum conditions were in the range of 80–85%.

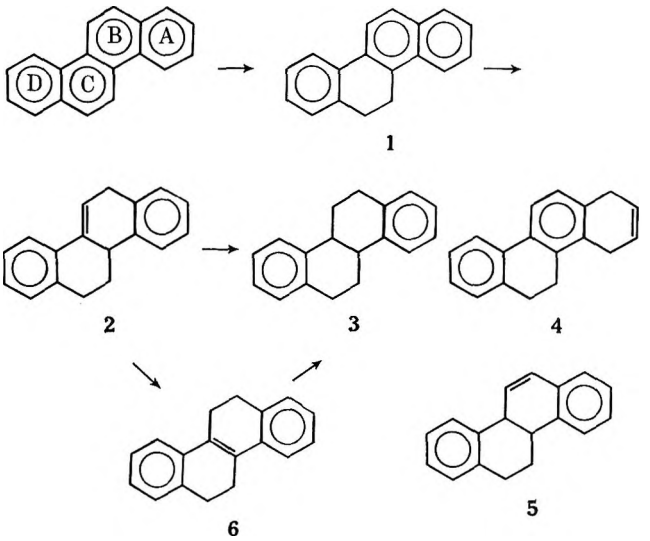
TABLE I
REDUCTION OF CHRYSENE BY ALKALI METALS IN LIQUID AMMONIA[a]

Expt	Metal (equiv)	Cosolvent (ml)	Method[b]	Product composition, %[c] Chrysene	Dihydro	Tetrahydro
1	Li (2.2)	None	A	30	9	61
2	Li (2.2)	THF (75)	A	19	38	43
3	Li (2.2)	THF (150)	A[d]	24	35	42
4	Na (2.2)	THF (75)	A	20	45	35
5	Ca (2.2)	THF (75)	A	38	10	52
6	Na (2.2)	DME (75)	A	50	18	31
7	Na (2.2)	THF (75)	B	25	69	7
8	Li (2.2)	THF (75)	B	25	50	24
9	Na (2.5)	THF (100)	B	9	82	9

[a] Reaction conditions are described in the Experimental Section. [b] The metal was added as a single piece in method A, and in four equal portions at 3-min intervals in method B. [c] Percentages refer to integrated peak values from glpc. [d] The amount of hydrocarbon was decreased from 5 to 2 mmol in this experiment only.

The nmr spectrum of the dihydro compound matched that of authentic 5,6-dihydrochrysene (**1**) prepared by ethanolysis of the chrysene–sodium adduct formed in dimethoxyethane according to the method of Hunt and Lindsey.[15] Samples of pure **1**, independent of their chemical origin, melted in a similar range (161.5–163°), 10° lower than reported[15] (171–173°); the discrepancy is apparently due to the presence of residual chrysene (detected by glpc) in samples purified by recrystallization from alcohol, the method employed by the earlier workers.

Further transformation to the tetrahydro stage, less obviously predictable, also proceeded regiospecifically to afford a tetrahydrochrysene. The latter was assigned the 4b,5,6,12-tetrahydrochrysene structure **2** on the basis of the nmr spectrum, the integrated proton ratios of which were inconsistent with the alternative structures, 1,4,5,6- and 4b,5,6,10b-tetrahydrochrysene[16] (**4** and **5**). Also, isomerization of **2** with



dilute methanolic HCl afforded the symmetrical isomer 5,6,11,12-tetrahydrochrysene (**6**), the structure of which was confirmed by independent synthesis.[17] The nmr spectrum of **6** exhibited a characteristic A_2B_2 pattern for 8 protons in the benzylic region in addition to an aromatic multiplet (8 H).

Preparatively, **2** was most conveniently obtained directly from chrysene *via* reduction with the calculated proportion of sodium or lithium. Concurrent reduction beyond this stage, though generally detected, was minimal in the absence of excess metal; with employment of even a large excess of sodium (8 equiv) in the presence of colloidal iron, less than 2% hexahydrochrysene was formed. The utility of iron in limiting reduction of certain hydrocarbons was noted earlier.[3,4]

A moderately stable tetrahydro anionic intermediate is suggested by the relative resistance of **2** to further reduction following its formation from **1**. This was confirmed by analogous reductive methylation with lithium and methyl bromide in ammonia. Glpc analysis of the product revealed three major compo-

(11) E. Clar, "Polycyclic Hydrocarbons," Vol. I, Academic Press, New York, N. Y., 1964, p 249; S. Friedman, M. L. Kaufman, and I. Wender, *J. Org. Chem.*, **36**, 694 (1971).

(12) J. D. Brooks, R. A. Durie, and H. Silberman, *Aust. J. Chem.*, **17**, 55 (1964).

(13) The closely related 9,10-dihydrophenanthrene dianion and/or radical anion was earlier demonstrated[4] to undergo rapid protonation by ammonia.

(14) Not only is the oxidation potential of Na lower than that of Li or Ca, but the solubility of the corresponding amide is considerably greater than those of $LiNH_2$ or $Ca(NH_2)_2$ [important in the protonation equilibrium: $(Ar^-M^+) + NH_3 \rightleftharpoons ArH + (M^+NH_2^-)$].

(15) S. E. Hunt and A. S. Lindsey, *J. Chem. Soc.*, 2227 (1958).

(16) In contrast, reductive methylation of 2-phenylnaphthalene with lithium in ammonia and methyl bromide furnished as the major product, 2-methyl-2-phenyl-1,2-dihydronaphthalene, analogous to **6**: unpublished results.

(17) E. Cahana, G. Schmidt, and K. Shah, *J. Org. Chem.*, **24**, 557 (1959).

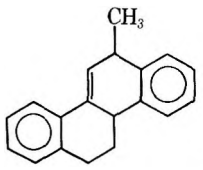
TABLE II

REDUCTION OF TETRAHYDROCHRYSENE[a]

Isomer	Metal	Cosolvent	Temp, °C	Method[b]	Quench	Time, min	Product composition, %[c] cis-3	trans-3	2 or 6
2	Na	THF[d]	−33	B	NH_4Cl	20	66	33	
2	Li	THF[d]	−33	B	NH_4Cl	20	64	34	2
2	Na	ether[e]	−33	B	NH_4Cl	20	64	34	2
2	Li	ether[e]	−33	B	NH_4Cl	20	65	34	1
2	Na	ether[e]	−33	A	NH_4Cl	20	66	33	
2	Na	ether[e]	−78	A	NH_4Cl	20	66	33	
2	Na	ether[e]	−78	A	H_2O	20	80	20	
2	Li	ether[e]	−78	A	H_2O	20	76	24	
2	Na	ether[e]	−33	A	*tert*-BuOH	20	75	24	
6	Na	ether[e]	−33	A	NH_4Cl	5	82	16	2
6	Li	THF[e]	−33	A	NH_4Cl	5	76	24	
6	Li	THF[e]	−33	A	H_2O	60	82	16	1
6	Li	THF[e]	−33	A	H_2O	5	79	18	
6	Na	THF[e]	−33	C	EtOH	3	49	36	13
Chrysene	Na	THF[d]	−33	B	NH_4Cl	20	66	33	1

[a] Reaction conditions are described in the Experimental Section. [b] The metal was added as a single piece in methods A and C, and in four equal portions at 3-min intervals in method B; alcohol (1 ml) was added to the solution before the metal in method C. [c] Percentages refer to integrated peak values from glpc. [d] Volume of cosolvent = 100 ml. [e] Volume of cosolvent = 70 ml.

nents characterized as 12-methyl-4b,5,6,12-tetrahydrochrysene (**7**, 48%), 10b-methyl-4b,5,6,10b-tetra-



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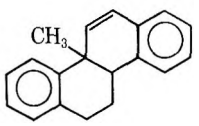

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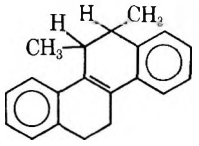

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hydrochrysene (**8**, 21%), and 5,6-dimethyl-5,6,11,-12-tetrahydrochrysene (**9**, 15%) by nmr analysis of samples trapped off the glpc column. The predominance of monomethylated derivatives is consistent with existence of a monoanion of **2** as the major stable intermediate species in ammonia (see Discussion). The dimethylated produce **9** may arise from a dianion or from **7** through abstraction of the proton at the 4b position by amide ion and methylation of the resulting allylic anion at the more accessible 11 position.

The stereochemical course of reduction of the tetrahydro isomers **2** and **6** is of particular interest. Although numerous examples of metal–ammonia reduction of cyclic styrenoid and stilbenoid olefins are found in the literature,[18] the majority involve natural products or related molecules of complex structure for which the observed steric course is variable and the factors controlling the stereochemistry are poorly understood. Reduction of both **2** and **6** with lithium or sodium proceeded smoothly and quantitatively to afford *cis*- and *trans*-4b,5,6,10b,11,12-hexahydrochrysene (**3**). A marked preference for one stereoisomer was observed under all conditions (Table II). The predominant isomer was assigned the cis structure on the basis of its lower melting point [69–70° (lit.[19] 75°)] compared with that of the trans isomer [114–115° (lit.[19,20] 112–114°, 115°)]. In the nmr spectra, deshielding due to steric crowding between the C-4 and equatorial C-5 protons, expected to be greater in the trans than the cis isomer,[21] was evident in the aromatic region of only the higher melting isomer, further confirming the structural assignment. Interestingly, reaction of the styrenoid structure **2** under a variety of conditions (quenched with ammonium chloride) afforded a lower cis–trans ratio (2:1) than analogous transformation of **6** for which the cis–trans ratio ranged from 3:1 to 5:1. With less efficient quenching agents, water or *tert*-butyl alcohol, **2** gave cis–trans ratios in the higher range. In contrast, reduction of **6** under Birch conditions (*i.e.*, alcohol present initially) resulted in markedly diminished cis steric preference (Table II).

Variation of solvent, metal, or temperature had no significant effect on these ratios, indicating ion pairing to be of little importance in determining product stereochemistry. Equilibration of the trans isomer with sodamide in refluxing ammonia afforded 86% *cis*-**3** and 14% *trans*-**3** at equilibrium (25 hr required). Insofar as the observed cis–trans ratios differ from this thermodynamic equilibrium proportion, they would appear to be kinetically determined (see Discussion).

Direct conversion of chrysene to **3** was possible with employment of large excess of sodium metal (10 g-atoms); the yield was virtually quantitative, with the only other discernible product being **2** (1%). By comparison, reduction of chrysene with a large excess of sodium in refluxing isoamyl alcohol furnished *cis*-**3** (22%), *trans*-**3** (38%), and tetrahydro isomers **2** plus **6** (40%). Further treatment with more sodium in fresh isoamyl alcohol failed to very appreciably alter these percentages. It appears, therefore, that the cis–trans ratio is altered to favor the trans isomer at elevated temperature and that complete conversion to the hexahydro level is not favored under these conditions.

Discussion

Thus chrysene, like all other polycyclic aromatic hydrocarbons investigated to date (naphthalene,[10] anthracene,[3,22] phenanthrene,[4] benz[*a*]anthracene,[3] tet-

(18) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. I, part 2, Wiley, New York, N. Y., 1963.

(19) A. D. Jarrett and J. D. Loudon, *J. Chem. Soc.*, 4052 (1955).

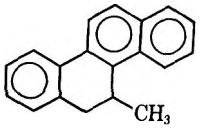
(20) G. Ramage and R. Robinson, *ibid.*, 607 (1933).

(21) W. Nagata, T. Terasawa and K. Tori, *J. Amer. Chem. Soc.*, **86**, 3746 (1964).

(22) R. G. Harvey and K. Urberg, *J. Org. Chem.*, **33**, 2570 (1968).

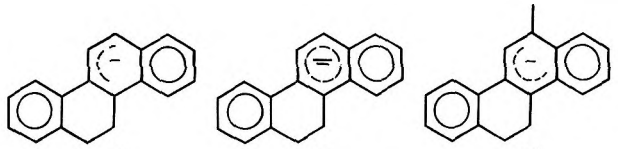
racene,[3] dibenz[a,h]anthracene,[3] pyrene,[1] and numerous alkyl derivatives), undergoes metal–ammonia reduction regiospecifically at each stage. Preferential reduction of the B ring rather than the A ring of **1** at the second stage is somewhat surprising. However, dihydrochrysene is essentially a bridged 2-phenylnaphthalene, and influence of the D ring is sufficient, apparently, to overcome the counter effect of alkyl substitution in the B ring.

Facile protonation of the dihydrochrysene radical anion and/or dianion by ammonia, as indicated by the observed ease of reduction beyond this stage, is consistent with the pK_a of the benzylic anion ($pK_a \sim 37$) relative to that of ammonia ($pK_a \sim 34$). The related 9,10-dihydrophenanthrene intermediate was earlier demonstrated to be rapidly protonated by ammonia.[4] Principal evidence for this was the failure to undergo alkylation under conditions wherein other benzylic anions undergo efficient reaction. Analogous treatment of the dilithiochrysene adduct in ammonia with methyl bromide led, unexpectedly, to formation of a methylated derivative of dihydrochrysene (60%). The nmr spectrum exhibited a single methyl doublet (3 H) at δ 1.13 (J = 7 Hz) in addition to the appropriate number of benzylic and aromatic protons (3 H and 10 H, respectively) for a monomethyldihydrochrysene. The latter was assigned the 5-methyl structure **10** on the basis of its dehydrogenation with trityl fluoroborate[23] in acetic acid to 5-methylchrysene. Apparently, therefore, the intermediate 5,6-dihydro-5-chrysenyl monoanion persists in liquid ammonia, and the protonation equilibrium ($ArH^- + NH_3 \rightleftharpoons ArH_2 + H_2N^-$) is readily shifted to the right by further reduction.



10

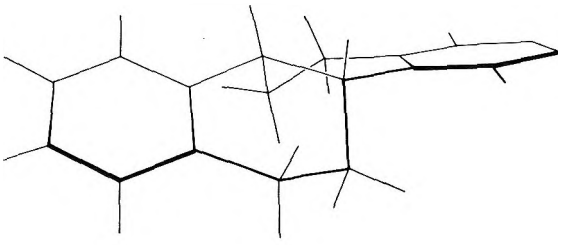
Although a moderately stable tetrahydro monoanionic intermediate such as **12** provides the simplest explanation for the origin of the monomethyl compounds **7** and **8**, a dianion mechanism may not be entirely rejected. Thus a dianion such as **13** may be considered to react rapidly at C-12 to furnish a monoalkyl monoanion, **14**, which either undergoes rapid protonation by the medium or is very much less reactive with respect to further alkylation and persists until reaction is quenched. Also, solvent-separated and/or contact ion pairs of differing reactivity may be involved, as suggested earlier for the naphthalene ring system.[10] Definitive answer to these questions lies beyond the scope of the present inquiry.



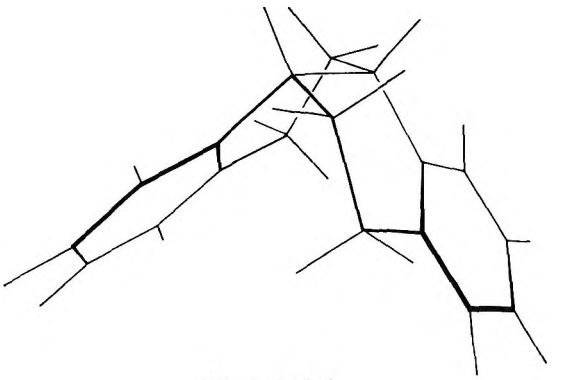
12 **13** **14**

The observed cis stereoselectivity of reduction of **2** and **6** contrasts markedly with the reported nonstereoselective transformation of closely related compounds. The most relevant case is the reported nonstereoselective reduction of 1,8- and 2,8-dimethoxy-2 with sodium and ethanol in ammonia by Birch and Smith.[24] Product stereochemistry is presumably determined during final protonation of the monoanion of **3**. According to Smith,[18] at least two factors may be considered to exert a controlling influence, a *conformational factor* involving the relative stabilities of the available conformations of the anion and a *steric approach factor* involving the relative accessibility of the anion to the proton donor in these conformations.

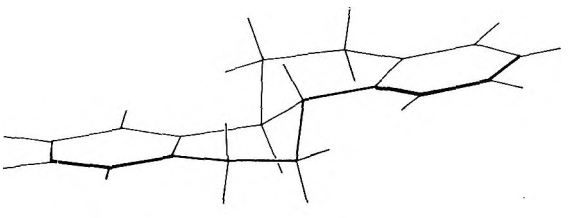
Consider first the conformational properties of hexahydrochrysene. Molecular models indicate three conformations for *trans*-**3**, a boat–boat, a boat–chair, and a chair–chair form, and two sets of three similar configurations for *cis*-**3**, a "folded" set and a "twisted" set. Steric interactions appear roughly comparable for the corresponding members of each of these three sets of conformers, and the chair–chair forms (**15**)



15a, *cis* twisted



15b, *cis* folded



15c, *trans*

represent energy minima in all cases. Therefore, on a simple statistical basis one might expect a cis–trans ratio of 2:1 at equilibrium; the observed proportion was 86% cis at −33°. The conformational preference of the monoanion will be a compromise between maximum overlap of the benzylic anion orbital with the aromatic π system and minimum steric interaction elsewhere. Since the geometry of the twisted chair–chair configuration **15a** appears to permit essentially zero overlap, this conformation may be eliminated from

(23) W. Bonthrone and D. H. Reid, *J. Chem. Soc.*, 2773 (1959).

(24) A. J. Birch and H. Smith, *ibid.*, 1882 (1951); 4909 (1956).

consideration. Although the remaining cis and trans chair–chair forms (**15b,c**) allow satisfactory orbital overlap, steric hindrance to approach of the proton donor is somewhat less to the folded cis conformer **15b** than to the more nearly planar trans conformer **15c**. Accordingly, a modest predominance of the former isomer may be predicted; experimentally 64–82% cis was observed.

The observed dependence of stereoselectivity on the structure of the olefin **2** or **6** and the efficiency of the quenching agent requires additional explanation. The latter effect may be rationalized as due to equilibration in the presence of the more strongly basic anions generated with employment of water or *tert*-BuOH as quenching agents. The former effect, however, cannot be accommodated in current concepts and involvement of an ion-pair factor seems likely. In this concept, the steric requirements of the counterions may be expected to dictate different structures for the respective intermediate dianions (from **2** and **6**), rapid protonation of which by ammonia[25] would lead to different stereoisomers. A cis-directing effect of ion pairing on the reduction of 1,3-dienes[26] and diphenylacetylene[27] has earlier been proposed.

Experimental Section

Physical Data.—Proton nmr spectra were obtained on a Varian A-60 spectrometer; chemical shifts are reported relative to TMS in $CDCl_3$ or CCl_4. Gas chromatographic analyses were performed on a F & M Model 500 chromatograph employing either a 4 ft × 0.25 in. 5% Apiezon L on 60–80 mesh Chromosorb W column (A) or a 6 ft × 0.25 in. 5% FFAP on 70–80 mesh Varaport 30 column (B) at 200° and 40-psi helium pressure. The latter column, employed in all the later work, afforded most efficient separations; retention times of **1**, **2**, *trans*-**3**, and *cis*-**3** were 17.8, 11.2, 7.1, and 5.4 min, respectively. Quantitative glpc data were verified by internal standard.

Metal–Ammonia Reduction.—Precautions for the exclusion of impurities (moisture, air, peroxides, ferrous metals) were scrupulously observed; all reductions with lithium were carried out under helium (passed through a drying tower containing Drierite and Ascarite) rather than nitrogen for reasons stated earlier.[2,3] Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were freshly distilled from $LiAlH_4$ before use. Ammonia was distilled into the reaction vessel through a column of barium oxide (10–20 mesh). Lithium wire (Lithium Corp. of America) was wiped free of oil and washed with hexane immediately before use. All reductions were carried out in a Morton flask equipped with a Dry Ice condenser, employing the conditions described for reduction of chrysene to **1**, unless specified otherwise.

5,6-Dihydrochrysene (**1**).—A solution of chrysene (1.14 g, 5 mmol) in 100 ml of THF was added to 150 ml of refluxing ammonia. To the resulting suspension was added sodium metal (12.5 mg-atoms) in four approximately equal pieces at 3-min intervals. After a total reaction time of 20 min, the intense blue color was discharged by addition of excess NH_4Cl (20 g) as rapidly as possible. Glpc analysis (column A) of the crude product showed **1** (82%) along with chrysene (9%) and **2** (9%). Chromatography on alumina gave pure **1**, mp 161.5–163°; the nmr spectrum showed aryl and benzylic protons (A_2B_2 pattern at δ 3.13) in the expected ratio.

Authentic **1** was prepared *via* alcoholysis of the disodiochrysene adduct formed in DME by a modification of the procedure of Hunt and Lindsey.[15] Yields considerably higher (*ca.* 80%) than previously reported[15] (35%) were obtained from reactions conducted in minimum solvent volume. In a typical reaction, a chilled suspension of chrysene (2.28 g, 10 mmol) in DME (10 ml) was treated with sodium dispersion (40% in mineral oil, 0.50 g of Na, 22 mmol) under nitrogen. The resulting deep green solution was stirred at ambient temperature for 3 hr and then decomposed by the rapid addition of excess ethanol. Glpc analysis of the crude product gave chrysene (7%), **1** (81%), *trans*-**3** (5%), and *cis*-**3** (6%). Chromatography on alumina gave pure **1**, mp 161.5–163°, the nmr spectrum of which agreed with that of **1** obtained by reduction in ammonia. *Note:* the stabilized commercial sodium must be employed as supplied, since washing with organic solvents prior to use greatly diminishes activity.

4b,5,6,12-Tetrahydrochrysene (**2**). **A. From Chrysene.**—To a stirred solution of anhydrous $FeCl_3$ (40 mg) in 150 ml of refluxing ammonia was added a solution of chrysene (1.14 g, 5 mmol) in 100 ml of THF. Sodium (40 mg-atoms) was added to the resulting stirred suspension in four approximately equal pieces at 3-min intervals. The color of the ensuing solution became initially deep green, then blue, and finally a characteristic deep purple. Reaction was quenched with NH_4Cl (20 g) 20 min after addition of the first piece of metal. Partition of the product between water and ether, followed by conventional work-up procedures, afforded 1.03 g of a product containing **2** (80%), **1** (15%), **3** (1%), and chrysene (4%) by glpc analysis on column A. Recrystallization from alcohol furnished pure **2**, mp 79–80°. The nmr spectrum was complex, exhibiting aromatic, benzylic, vinyl, and aliphatic protons in the expected ratios; the vinyl protons appeared as a triplet at δ 6.4 (J = 3 Hz), and the benzylic protons occurred as multiplets centered at δ 2.6 (3 H) and 3.1 (2 H).

Anal. Calcd for $C_{18}H_{16}$: C, 93.05; H, 6.94. Found: C, 93.06; H, 6.83.

B. From Dihydrochrysene.—To 50 ml of refluxing ammonia was added consecutively a solution of **1** (2.5 mmol) in THF (25 ml), $FeCl_3$ (10 mg), and lithium metal (8.75 mg-atoms). The resulting purple solution was stirred at reflux for 1 hr, then decomposed with water, and worked up by the usual procedure to afford almost pure (by nmr) **2**, recrystallization of which from methanol gave **2**, mp 79–80°.

Isomerization of 2 to 6.—A solution of **2** (1.14 g) and *p*-toluensulfonic acid (200 mg) in ethanol (10 ml) was heated at reflux for 3 hr, then treated with 5% aqueous $NaHCO_3$, extracted with ether, dried, and evaporated to furnish 1.10 g of **6**. Recrystallization from methanol furnished pure **6**, mp 106–107° (lit.[15] 105°); the nmr spectrum displayed the expected aryl (8 H), benzylic (4 H), and allylic (4 H) protons, the latter as an A_2B_2 pattern centered at δ 2.8.

***cis*- and *trans*-4b,5,6,10b,11,12-Hexahydrochrysene** (**3**). **A. From 6.**—A solution of **6** (0.53 g, 2.4 mmol) in 35 ml of anhydrous ether was added to 75 ml of refluxing ammonia. To this was added sodium metal (0.14 g, 6 g-atoms) with efficient stirring. Reaction was quenched after 5 min with excess NH_4Cl (10 g). Work-up by the usual method provided *cis*- and *trans*-**3**, 82 and 16%, respectively. Samples trapped off the glpc column (B) melted at 69–70 and 114–115°, respectively (lit.[19,20] 75 and 112–114°, 115° for *cis*- and *trans*-**3**, respectively). The nmr spectra were complex, exhibiting aromatic, benzylic, and aliphatic protons in the expected ratios. Pure *cis*-**3** in larger quantity was conveniently obtained by recrystallization from alcohol; pure *trans*-**3** was isolated from chromatography of the mother liquors on alumina.

B. From 2.—Analogous reaction of **2** afforded *cis*- and *trans*-**3** in 2:1 ratio. See Table II for other examples.

C. From Chrysene.—Direct reduction of chrysene to the hexahydro stage was efficiently achieved with excess sodium (10 g-atoms) in ammonia. See Table II.

Reductive Methylation of Chrysene. A. 5-Methyl-5,6-dihydrochrysene (**10**).—The blue solution formed upon interaction of sodium with chrysene in THF–ammonia (by the method described for synthesis of **1**) was decolorized after 20 min with methyl bromide gas and then decomposed with excess NH_4Cl. Glpc analysis (column B) indicated **1** (23%) and **10** (65%) as the major product components. The 5-methyl-5,6-dihydro structure was assigned **10** on the basis of its conversion to 5-methylchrysene, mp 117–118° (lit.[28] 117.2–117.8°), with trityl fluoroborate in acetic acid.[23] 5-Methylchrysene was obtained free of chrysene by chromatography on alumina. The nmr spectrum of **10** exhibited a methyl doublet at δ 1.1 (J = 8 Hz); the methyl group of 5-methylchrysene appeared at δ 3.15.

(25) Attempts to trap an intermediate dianion with methyl bromide afforded only **3**, indicating absence of any appreciable concentration of mono- or dinegative ions of hexahydrochrysene in ammonia after 20 min at −33°.

(26) N. L. Bauld, *J. Amer. Chem. Soc.*, **84**, 4347 (1962).

(27) G. Levin, J. Jagur-Grodzinski, and M. Szwarc, *J. Org. Chem.*, **35**, 1702 (1970).

(28) L. F. Fieser and L. M. Joshel, *J. Amer. Chem. Soc.*, **62**, 1214 (1940); M. S. Newman, *ibid.*, **62**, 873 (1940).

B. Mono- and Dimethyltetrahydrochrysene (7, 8, and 9).—Reductive methylation of chrysene utilizing a procedure analogous to that employed for reduction to the tetrahydro stage afforded a complex product mixture. Major components **7** (48%), **8** (21%), and **9** (15%) were trapped off the glpc column and identified by nmr and mass spectrometry. The integrated proton nmr spectra were consistent with the assigned structures. In particular, the spectrum of **7** exhibited a methyl doublet at δ 1.33 (J = 7 Hz, 3 H) and a vinyl resonance at δ 6.30 (d, J = 4 Hz with fine splitting, 1 H); the spectrum of **8** had a methyl singlet at δ 0.95 (3 H) and vinyl protons as a pair of doublets (2 H) at δ 6.63 (J = 10 Hz) and 6.42 (J = 9 Hz), respectively; and the spectrum of **9** contained overlapping methyl doublets at δ 1.05 (J = 7 Hz, 3 H) and 1.18 (J = 7 Hz, 3 H). Alternative structures derived from **10**, *e.g.*, 5-methyl-4b,5,6,12-tetrahydrochrysene, were ruled out by the fact that analogous reductive methylation of **1** also provided the same three major products.

Equilibration of 3.—A solution of *trans*-**3** (200 mg) in 75 ml of THF was added to a solution of sodamide (from 980 mg of sodium and 40 mg of $FeCl_3$) in 120 ml of liquid ammonia and stirred at reflux for 3 hr. Conventional work-up provided recovered **3**. Repetition at various time intervals led to the following cis–trans ratios by glpc analysis.

Time, hr	% cis	% trans
3	20	80
8.5	50	50
15	75	25
21.5	85	15
25	86	14

Registry No.—**2**, 31570-60-2; *cis*-**3**, 31579-69-8; *trans*-**3**, 31579-70-1; **6**, 18930-97-7; chrysene, 218-01-9.

Acknowledgment.—The invaluable technical assistance of Miss Leonida Arzadon and Mrs. Cecilia N. Cortez is gratefully acknowledged.

Stereochemistry of the Addition of Methylzinc and -cadmium Reagents to Acyclic Aldehydes[1a]

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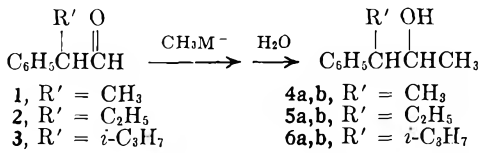
The reactivity and stereochemistry of addition of methyl Grignard and Cd and Zn reagents toward 2-phenylpropanal (**1**), 2-phenylbutanal (**2**), and 2-phenyl-3-methylbutanal (**3**) have been determined. The reactivity of *in situ* dimethylcadmium and -zinc reagents containing magnesium halide was comparable to that of the Grignards. The lower stereoselectivity observed with the cadmium and especially the zinc reagents toward **1** and **2** has been rationalized as resulting from a tight four-center transition state for such reactions. The anomalous results obtained for the addition of the methyl reagents to 2-phenyl-3-methylbutanal represent a violation of the postulates of Cram, Karabatsos, and Felkin.

In our continuing study of the addition reactions of *in situ* alkylzinc and -cadmium reagents, we have determined the stereochemistry of addition of various methyl reagents to a series of 2-phenylalkanals (**1**, **2**, and **3**). The stereochemistry of addition of isopropylmagnesium bromide to **3** has also been determined. The per cent stereoselectivity obtained with the various organometallic reagents was determined by glpc analysis with racemic reagents.



1, R′ = CH_3; **2**, R′ = C_2H_5; **3**, R′ = *i*-C_3H_7

4a,b, R′ = CH_3; **5a,b**, R′ = C_2H_5; **6a,b**, R′ = *i*-C_3H_7

$\binom{R,S}{S,R}$ threo; $\binom{S,S}{R,R}$ erythro

a b

The absolute configurations of threo and erythro isomers of **4** and **5**, as well as those obtained from the reaction of isopropylmagnesium bromide with **3**, are known.[2] The identification of *threo*- and *erythro*-3-phenyl-4-methyl-2-pentanols (**6**) resulting from addition of methylmagnesium iodide to **3** is based on their order of elution on STAP and FFAP, their relative rates of dehydration, and their characteristic infrared spectra (see Experimental Section).

From an inspection of Table I it is evident that, for all threo–erythro pairs, the threo isomer possesses the shorter retention time (entries 3, 5, and 8). On this basis entry 10 is assigned the threo configuration. Thermal dehydration (see Experimental Section) of all threo–erythro pairs in the presence of zinc bromide indicated that the alcohol of longer retention time (erythro) in each instance underwent dehydration at the faster rate. A study of the rate of solvolysis of *threo*- and *erythro*-3-phenyl-2-butanols (**4**) by Cram[3] has revealed that the erythro isomer reacts at a faster rate than the threo isomer. All the threo and erythro isomers obtained by preparative glpc are consistent with the above assignments.

Results

From the results compiled in Table II, certain general observations can be made.

(1) On the basis of unchanged aldehyde, the reactivity of $(CH_3)_2M$ (M = Zn, Cd) toward the various aldehydes is greater than that toward 4-*tert*-butylcyclohexanone,[4] and is essentially equivalent to that of the Grignard reagents. The reactivity of organozinc reagents prepared from methyllithium is extremely low.

(2) The stereochemistry of addition of Grignard reagents to acyclic aldehydes is independent of concentration (association). CH_3MgBr is more stereoselective than CH_3MgI. By contrast, the stereochemistry of addition of zinc and cadmium reagents,

(1) (a) Taken in part from Ph.D. theses of E. J. G. and W. J. K., University of New Hampshire, 1969. (b) National Defense Education Act Fellow, 1966–1969. (c) Nationl Science Foundation Trainee, 1966–1969.

(2) G. J. Karabatsos, *J. Amer. Chem. Soc.*, **89**, 1367 (1967).

(3) D. J. Cram, H. L. Nyquist, and F. A. Abd Elhafez, *ibid.*, **79**, 2876 (1957).

(4) P. R. Jones, E. J. Goller, and W. J. Kauffman, *J. Org. Chem.*, **34**, 3566 (1969).

TABLE I

GLPC ANALAYSES OF ALDEHYDES AND THREO AND ERYTHRO ALCOHOLS

Entry	Compd	Registry no.	Liquid phase	Temp, °C	Flow rate, ml/min	Retention time, min
1	$PhC(CH_3)HCHO$		FFAP	150	67	9.5
2	*threo*-$PhC(CH_3)HC(CH_3)HOH$	1502-80-3	FFAP	150	67	17.2
			Carbowax 20M	150	67	20.4
3	*erythro*-$PhC(CH_3)HC(CH_3)HOH$	1502-79-0	FFAP	150	67	20.6
			Carbowax 20M	150	67	24.5
4	PhC(Et)HCHO		FFAP	150	67	9.6
5	*threo*-PhC(Et)HC(CH_3)HOH	6932-55-4	FFAP	150	67	16.1
6	*erythro*-PhC(Et)HC(CH_3)HOH	6932-54-3	FFAP	150	67	19.8
7	PhC(*i*-Pr)HCHO		FFAP	160	67	9.0
			STAP	160	70	9.8
8	*threo*-PhC(*i*-Pr)HC(*i*-Pr)HOH	6932-58-7	Carbowax 20M	150	70	42.6
9	*erythro*-PhC(*i*-Pr)HC(*i*-Pr)HOH	6932-57-6	Carbowax 20M	150	70	47.1
10	*threo*-PhC(*i*-Pr)HC(CH_3)HOH	31330-87-7	FFAP	160	67	13.4
			STAP	160	70	21.6
11	*erythro*-PhC(*i*-Pr)HC(CH_3)HOH	31330-88-8	FFAP	160	67	17.2
			STAP	160	70	27.6

TABLE II[a]

REACTION OF ORGANOMETALLIC REAGENTS WITH $C_6H_5C(R')HCHO$

Entry	R′	Reagent	Concn, *M*	% erythro[b,c]	% unchanged aldehyde[d]
1	CH_3	CH_3MgI	0.8	64.3	<1
2	CH_3	CH_3MgI	0.1	65.6	<1
3	CH_3	CH_3MgBr	0.8	69.5	<1
4	CH_3	$(CH_3)_2Cd$ (I, I)[e]	0.4	61.1	<1
5	CH_3	$(CH_3)_2Cd$ (Br, Br)[f]	0.4	59.8	<1
6	CH_3	$(CH_3)_2Cd$ (I, Cl)	0.4	60.4	<1
7	CH_3	$(CH_3)_2Cd$ (I, Cl)	0.4	62.1	<1
8	CH_3	CH_3CdX (I, Cl)[g]	0.8	56.8	<1
9	CH_3	CH_3CdBr (Br, Br)	0.8	62.2	<1
10	CH_3	CH_3CdI (I, I)	0.8	60.8	<1
11	CH_3	$(CH_3)_2Zn$ (I, I)	0.3	54.7	<1
12	CH_3	$(CH_3)_2Zn$ (Br, Br)	0.3	56.9	<1
13	CH_3	$(CH_3)_2Zn$ (I, Cl)	0.3	51.5	8
14	CH_3	CH_3ZnI (I, I)	0.3	54.3	<1
15	CH_3	CH_3ZnBr (Br, Br)	0.3	56.0	2
16	CH_3	CH_3ZnX (Br, I)	0.3	54.1	2
17	CH_3	CH_3ZnX (I, Cl)	0.3	59.7	40
18	CH_3	CH_3ZnX (CH_3Li, ZnI_2)	0.3	53.5	75
19	CH_3	CH_3ZnX (CH_3Li, $ZnBr_2$)	0.3		90
20	C_2H_5	CH_3MgI	0.8	65.2	<1
21	C_2H_5	CH_3MgBr	0.8	70.8	<1
22	C_2H_5	$(CH_3)_2Cd$ (Br, Br)	0.4	58.4	<1
23	C_2H_5	$(CH_3)_2Zn$ (I, I)	0.3	54.5	<1
24	*i*-C_3H_7	CH_3MgI	0.8	44.9	<1
25	*i*-C_3H_7	$(CH_3)_2Cd$ (I, I)	0.4	32.5	<1
26	*i*-C_3H_7	$(CH_3)_2Cd$ (I, Br)	0.4	29.3	<1
27	*i*-C_3H_7	$(CH_3)_2Zn$ (I, I)	0.3	36.3	<1
28	*i*-C_3H_7	*i*-PrMgBr	0.8	64.2	<1

[a] The ratio of organometallic to aldehyde was 1:1 unless otherwise noted. [b] Normalized %; % threo + % erythro = 100. [c] Results reproducible within ±1% in separate reaction runs. [d] % = $area_{aldehyde}/(area_{aldehyde} + area_{alcohols}) \times 100$. [e] Halogens in parentheses indicate, respectively, the methyl halide from which RMgX was prepared and the metal halide used for the exchange. [f] Zinc bromide solution was prepared from commercially available salt. [g] Ratio of organometallic to aldehyde was 2:1.

except those designated as (I, Cl), is independent of halide.

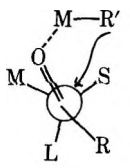
(3) Erythro alcohol is the major product of addition of the organometallics to 2-phenylpropanal and 2-phenylbutanal, the per cent erythro isomer being dependent on organometallic and independent of aldehyde. Threo alcohol is the major product of addition of methyl reagents (not *i*-PrMgBr) to 2-phenyl-3-methylbutanal.

(4) Except for the reactions with 2-phenyl-3-methylbutanal, the per cent erythro alcohol decreases according to the series $CH_3MgX > (CH_3)_2Cd$, $CH_3CdX > (CH_3)_2Zn$, CH_3ZnX. The dimethylzinc reagents are less stereoselective than are the cadmiums toward all aldehydes studied.

(5) Changing the magnesium reagent from methyl to isopropyl in reactions with 2-phenyl-3-methylbutanal causes an inversion in stereoselectivity (44.9% erythro *vs.* 64.2% erythro, respectively).

Classically, the stereochemistry of addition reactions of organometallic reagents to acyclic aldehydes containing an asymmetric carbon has been rationalized

by Cram's rule.[5] Although the diastereomeric product distribution for a large number of nucleophilic addition reactions has been correctly predicted qualitatively by the Cram model **7**, Karabatsos[2] has recently pointed out a number of shortcomings from a quantitative



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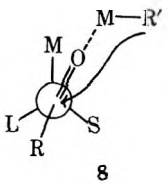
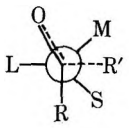


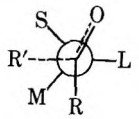
8

standpoint. The Karabatsos treatment, somewhat less empirical than that of Cram, is based on two assumptions which lead to the conclusion that the favored transition-state conformation may be represented by **8**. Unlike Cram, Karabatsos predicts the degree of stereoselectivity of the addition reactions to be independent of the steric bulk of the attacking reagent R′ but to decrease as the steric bulk of R increases.

Felkin and coworkers[6] have attempted to show that the interpretation of the steric outcome of the nucleophilic addition reactions can encompass both open-chain carbonyls and cyclohexanones. According to Felkin, the importance of torsional strain in the transition states for acyclic systems requires that staggered (**9**, **10**, and **11**) rather than eclipsed (**7** and **8**) conformations be considered. Given certain basic assumptions,[6] **9** is considered to represent the lowest energy transition state. Contrary to the prediction of Karabatsos, one would expect, on the basis of **9**, **10**, and **11**, an increase in the stereoselectivity of the reaction as the steric bulk of M, L, or R increases.



9



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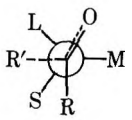
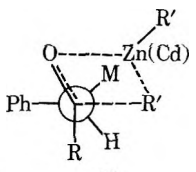
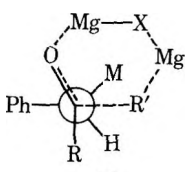


11

In view of the recent success of the Felkin approach to explain the stereochemistry of addition reactions in cyclic and acyclic systems, the results outlined above will be discussed primarily in terms of transition state conformers **9**, **10**, and **11**. Our earlier hypothesis[4] that the zinc and cadmium additions can be visualized as involving a bridged, four-center transition state leads more specifically to contrasting structures **12** and **13** for the transition states for zinc or cadmium and



12



13

magnesium, respectively. The observed trend in stereoselectivity with a change in metal, absence of halide dependence on the stereochemistry for zinc and cadmium reactions, and the inertness of Me_2Zn and Me_2Cd reagents prepared from MeLi are all characteristics consistent[4] with the four-center transition state.

(5) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 69.

(6) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968).

With a given organometallic series, the stereochemistry of addition was essentially insensitive to the change of the medium group from methyl to ethyl (**1** and **2**) in the aldehyde substrate. The reaction of **3** with *i*-PrMgBr proceeds to give the erythro alcohol in 64.2% isomeric purity. However, an inversion in stereoselectivity was observed for the addition of methyl reagents to **3**, threo alcohol being the major product. This result represents a violation of the postulates of Cram, Karabatsos, and Felkin.

According to Felkin, the important steric interactions involve R′ and R (H). The interaction between complexed carbonyl oxygen and the substituents attached to the α carbon is believed to be insignificant.

Inspection of **12** and **13** reveals that, while interactions between a magnesium-coordinated carbonyl and M may be small, this need not be the case for zinc- or cadmium-coordinated species. If the four-center transition state is tighter, as previously postulated,[4] then cadmium and especially zinc reactions may be more sensitive to the steric bulk of M, destabilizing **9** relative to **10** (leading to more threo alcohol). Thus, modification of the Felkin model to include the M–O interactions would account for the greater proportion of threo alcohol obtained for Zn and Cd reactions and explain the observed stereoselectivity series Mg > Cd > Zn for reactions involving **1** and **2**. Both Cram and Karabatsos models would predict the opposite for a tighter four-center transition state. Additional support for this argument can be seen from consideration of entries 20 and 24 *vs.* 22 and 25 of Table II. The change in stereochemistry with increasing M is greater for the cadmium than for the magnesium reagents.

The fact that no change in stereoselectivity was observed as M varies from methyl to ethyl among the various organometallic reagents implies that either the M–H steric interactions (**10**) do not increase significantly or that the increase which does occur is counterbalanced by a similar increase in the magnitude of the M–O steric interactions (**9**).

Although it is tempting to extend the above arguments to explain the per cent threo alcohol (>50%) obtained through the interaction of the methyl reagents and 2-phenyl-3-methylbutanal, such rationalization appears untenable on the basis of existing data.[2] While the results agree qualitatively with the modified Felkin analysis described above, quantitatively they are less appealing. The experimentally determined free-energy difference of 0.31 kcal calculated from the threo/erythro ratio of 1.8 for **6** appears to be larger than expected.

An alternate suggestion might be that, when M = isopropyl, the phenyl group at the α carbon may be so orientated that steric and electronic interactions are reduced considerably toward the attacking methyl reagent. Thus isopropyl may act as the largest group in **9**, **10**, and **11**. Although such a model would predict threo alcohol as the major product from all organometallic reagents studied, one would expect the order of stereoselectivity of reagents to remain Mg > Cd > Zn and not the observed Cd > Zn > Mg.

It is clear that the results reported here fail to fit consistently any of the hypotheses proposed for the stereochemistry of addition reactions. Further exploration into the configurational composition of prod-

ucts from a wider variety of organometallics and acyclic carbonyl compounds is warranted.

Experimental Section

Several of the following experimental procedures are modeled closely after those described in previous papers.[4,7]

Preparation of 2-Phenylbutanoyl Chloride.—Thionyl chloride (224 g, 1.9 mol) was added slowly with stirring to 50 g (0.31 mol) of 2-phenylbutanoic acid. The mixture was refluxed for 1.5 hr and stirred for an additional 0.5 hr at room temperature. After removal of excess thionyl chloride at reduced pressure, 54 g (97%) of 2-phenylbutanoyl chloride was collected at 84–87° (3.7 mm) [lit.[8] bp 97–98° (14 mm)].

Preparation of the Imidazolide of 2-Phenylbutanoic Acid.[9]—To a solution of imidazole (40.4 g, 0.59 mol) in 300 ml of anhydrous THF was added, over a period of 30 min at room temperature, a solution of 54 g (0.29 mol) of 2-phenylbutanoyl chloride in 200 ml of THF. The contents were refluxed for 1 hr and stirred at room temperature for an additional 4 hr. Then the solution was cooled to 0° and the imidazole hydrochloride removed by filtration. After removal of the solvent *in vacuo*, the solid residue was washed with cold benzene and 45 g of white imidazolide collected by suction filtration. The benzene washings were extracted with dilute hydrochloric acid and saturated sodium bicarbonate and dried, and the benzene was removed *in vacuo* on a rotary evaporator. The solid residue was washed with an ice-cold petroleum ether (bp 30–60°)–benzene (3:1, v/v) solution and 10 g of white imidazolide was obtained. The combined product, mp 86.5–89° (lit.[10] mp 87–89°), weighed 55 g (87%). The ir spectrum of the imidazolide is characterized by a carbonyl band at 1730 cm^{-1}.

Preparation of 2-Phenylbutanal.—A procedure similar to that described by Staab[9] was employed. A solution of 55 g (0.26 mol) of the imidazolide of 2-phenylbutanoic acid in 250 ml of ether was cooled to −20° in an ethanol–snow bath. Then 2.7 g (0.07 mol) of lithium aluminum hydride in 200 ml of ether was added, with stirring, at such a rate that the temperature did not exceed −15°. After completion of the addition the reaction mixture was stirred at −20° for 0.5 hr and then allowed to reach ambient temperature. The reaction was carried out under an atmosphere of dry nitrogen. Hydrolysis was accomplished with 100 ml of dilute hydrochloric acid. The aqueous layer was extracted twice with ether, the ether layers were combined and dried, and the solvent was removed on a rotary evaporator. Distillation of the crude product gave 20.0 g {0.13 mol, 50% of 2-phenylbutanal, bp 50.5–59° (0.7 mm) [lit.[11] bp 97–99° (15 mm)]}.

Preparation of 2-Phenyl-3-methylbutanonitrile.—2-Phenyl-3-methylbutanonitrile [bp 110° (7 mm)] was prepared in 59% yield from phenylacetonitrile and isopropyl bromide in 50% aqueous sodium hydroxide according to the method of Makosza and Serafin.[12] The final product contained approximately 22% unchanged phenylacetonitrile.

Preparation of 2-Phenyl-3-methylbutanamide.—The reaction was carried out as previously described[13] with a solution of 106 g (0.67 mol) of nitrile, 270 ml of hydrogen peroxide (30%), 250 ml of ethanol, and 27 ml of 6 *N* sodium hydroxide. The crude, air-dried product weighed 93.7 g (79%), mp 93–103° (lit.[14] 111°). The ir spectrum was consistent with the assigned structure.

Preparation of 3-Methyl-2-phenylbutanoic Acid.—A solution of 20 g (0.11 mol) of the above amide, 60 ml of glacial acetic acid, 60 ml of concentrated HCl, and 20 ml of water was cooled to 0° by means of an ice–salt bath. A solution of 16 g of $NaNO_2$ (0.23 mol) in 30 ml of water was added dropwise over a period of 1.5 hr with stirring. After the addition was complete, the bath was removed and the mixture was stirred for 12 hr. It was then diluted with water and extracted twice with 100-ml portions of ether. The ether extracts were combined and extracted six times with 50 ml of saturated NaCl solution. The ether solution was dried and then concentrated on a rotary evaporator. Distillation yielded 13.1 g (65%) of acid product, bp 109–114° (0.7 mm).

Preparation of 2-Phenyl-3-methylbutanoyl Chloride.—The procedure described by Cram[3] was employed. 2-Phenyl-3-methylbutanoic acid (24.1 g, 0.135 mol) and 19.2 g (0.16 mol) of thionyl chloride were stirred overnight at room temperature. The excess thionyl chloride was removed at room temperature (20 mm). The desired acid chloride (23.7 g, 89%) was collected at 75–79° (1.4 mm) [lit.[3] bp 125° (13 mm)].

Preparation of 2-Phenyl-3-methylbutanal.—The procedure described by Brown[15] for the reduction of acid chlorides to aldehydes was employed. To a solution of 15.2 g (0.077 mol) of 2-phenyl-3-methylbutanoyl chloride in 50 ml of diglyme, cooled to −78°, was added 20.3 g (0.08 mol) of lithium aluminum tri-*tert*-butoxyhydride in 100 ml of diglyme over a period of 1 hr in a nitrogen atmosphere. The Dry Ice–acetone bath was removed and the mixture allowed to warm to room temperature (*ca.* 1 hr). Hydrolysis was accomplished by pouring the contents onto crushed ice, and the resultant mixture was extracted several times with ether. Extraction of the combined ether layers with aqueous sodium bisulfite failed to remove any of the aldehyde. The combined ether layers were then dried over $MgSO_4$, the solvent was removed on a rotary evaporator, and the residue distilled at 70–73° (1.6 mm) [lit.[16] bp 72–73° (1.0 mm)], to yield 5.0 g (33%) of 2-phenyl-3-methylbutanal.

Reaction of Methylmagnesium Bromide with 2-Phenylpropanal.—The following procedure will serve to illustrate the reaction of the various Grignard reagents with 2-phenylpropanal, 2-phenylbutanal, and 2-phenyl-3-methyl-butanal.

An ethereal solution of 14.5 ml of 2.07 *M* methylmagnesium bromide (0.03 mol) was added by means of a 20-ml syringe to 39 ml of anhydrous ether with stirring. The reagent was then cooled with an ice–salt bath and stirred until the internal temperature reached 0°. A solution of 2.0 g (0.015 mol) of 2-phenylpropanal in 15 ml of ether was added at such a rate that the temperature did not exceed 5°. The ether layer was separated and the aqueous layer extracted twice with ether. The combined ether layers were dried ($MgSO_4$) and the solvent was removed at room temperature on a rotary evaporator to give 2.0 g of crude product.

Glpc analysis was conducted on a 10 ft × 0.25 in. column packed with 10% FFAP on Chromosorb W at a temperature of 170° and a flow rate of 67 ml/min. The two major components of the reaction of methylmagnesium iodide and 2-phenylpropanal were collected by preparative glpc. The nmr spectra of the diastereomeric alcohols are in accord with published values:[17] nmr (CCl_4) (threo) δ 1.10, 1.22 (overlapping d, 6, $J \cong 7$ Hz, $(CH_3)_2CH$), 1.48 (s, 1, OH), 2.61 (m, 1, $CH_3(Ph)CH$), 3.70 (m, 1, $CH_3(OH)CH$), 7.15 (s, 5, Ph); (erythro) 0.92 (d, 3, $J \cong 8$ Hz, CH_3CHCH_3), 1.22 (d, 3, $J \cong 7$ Hz, CH_3CHCH_3), 2.58 (m, 1, $CH_3(Ph)CH$), 2.79 (s, 1, OH), 3.74 (m, 1, $CH_3(OH)CH$), and 7.14 ppm (s, 5, Ph). The chromatograms indicated in all cases a nearly quantitative conversion of aldehyde to a mixture of threo and erythro alcohols. The results obtained with the Grignard reagents (Table II) were reproducible within ±1% in separate reaction runs.

Separation and Identification of Diastereomers.—Identification of the threo and erythro alcohols obtained from addition of methyl Grignard reagents to 2-phenylpropanal and 2-phenylbutanal, as well as of threo and erythro alcohols obtained from addition of isopropylmagnesium bromide to 2-phenyl-3-methylbutanal, is based on previous literature reports[2] indicating that the major product is the erythro isomer. In addition, *threo*-3-phenyl-2-butanol (**4a**) was isolated *via* its monoacid phthalate,[18] while *erythro*-3-phenyl-2-butanol (**4b**) was obtained by column chromatography on neutral alumina (activity I) with pentane–ether as eluent. The identification of *threo*- and *erythro*-3-phenyl-4-methyl-2-pentanols (Table I, entries 10 and 11), resulting from

(7) P. R. Jones, W. J. Kauffman, and E. J. Goller, *J. Org. Chem.*, **36**, 186 (1971).

(8) I. M. Heilbron, A. H. Cook, H. M. Bunbury, and D. H. Hey, "Dictionary of Organic Compounds," Vol. IV, 4th ed, Oxford University Press, London, 1965, p 2677.

(9) H. A. Staab, *Angew. Chem.*, **74**, 407 (1962).

(10) K. P. Long, Ph.D. Thesis, University of New Hampshire, 1969.

(11) D. J. Cram and R. Davis, *J. Amer. Chem. Soc.*, **71**, 3871 (1949).

(12) M. Makosza and B. Serafin, *Rocz. Chem.*, **39**, 1595 (1965); *Chem. Abstr.*, **64**, 17475 (1966).

(13) C. R. Noller, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, 586.

(14) R. C. Weast, Ed., "Handbook of Chemistry and Physics," 47th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967.

(15) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **80**, 5377 (1958).

(16) D. J. Cram, F. A. Abd Elhafez, and H. L. Nyquist, *ibid.*, **76**, 22 (1954).

(17) C. A. Kingsbury and W. B. Thornton, *J. Org. Chem.*, **31**, 1000 (1966).

(18) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).

addition of methylmagnesium iodide to 2-phenyl-3-methylbutanal, follows from their order of elution on STAP and FFAP (Table I) and on their relative rates of dehydration (see below). The nmr spectra of the two diasteromeric alcohols were inconclusive for configurational assignment, but their infrared spectra[19] were characteristically distinct and bear close analogies with the other threo-erythro pairs. The alcohols 4–6 contain a weak OH stretching band at 3550–3570 cm^{-1}, assignable to nonbonded or π-bonded[19b] hydroxyl, which is better resolved and relatively stronger in the threo isomers 4a–6a. The range for the polymeric OH in the threo isomers is 3420–3430 cm^{-1}, whereas that in the erythro isomers is 3300–3380 cm^{-1}. A larger frequency shift between the two OH bands is observed with the erythro alcohols: $\Delta_{\nu(OH)}$ 4a, 140; 5a, 140; 6a, 140; 4b, 180; 5b, 180; 6b, 250 cm^{-1}. The greater strength of the polymeric hydrogen bond in the erythro isomers[19a] is attributed to conformational differences and less sterically crowded OH functions in these alcohols.[17]

Pure samples (>99%) of *threo*- and *erythro*-3-phenyl-2-butanol and 3-phenyl-4-methyl-2-pentanol were obtained by preparative glpc on FFAP (10%, Chromosorb W, 10 ft). The purity was determined by reinjection for analysis on FFAP and Carbowax 20M–TPA. The response ratios determined on Carbowax 20M–TPA are as follows: 4a/4b = 1.01 ± 0.01; 6a/6b = 1.01 ± 0.01.

Dehydration of Threo and Erythro Alcohols.—From an inspection of Table I it is clear that for all threo–erythro pairs, the threo isomer possesses the shorter retention time. The relative rates of dehydration of the various diastereomeric pairs of addition products were monitored by glpc analysis on STAP. The injector port of the chromatograph (265°) was coated with salt by injection of ether solutions of zinc bromide. Subsequent injection and analysis of the various diastereomeric product pairs (Table I) showed the appearance of several new peaks (presumably olefins) with retention times slightly longer than that of the ether solvent and an accompanying decrease in the amount of threo and erythro alcohols.

Comparison of the isomeric composition of the alcohol addition products before and after dehydration revealed that the alcohol of longer retention time (erythro) in each instance underwent dehydration faster than the isomer of shorter retention time (threo). Similar results were observed for solvolysis of the 3-phenyl-2-butanols[3] and give additional support to the assignment made for *threo*- and *erythro*-3-phenyl-4-methyl-2-pentanols (6a, 6b).

Reaction of *in Situ* Dimethylcadmium (I, Cl) with 2-Phenylpropanal.—The following procedure will serve to illustrate the reaction of the various *in situ* cadmium reagents (Table II) with 2-phenylpropanal, 2-phenylbutanal, and 2-phenyl-3-methylbutanal.

A solution of 15 ml of 2.0 *M* MeMgI (30 mmol) was added *via* a 20-ml syringe to a stirred, cold mixture of 2.74 g of $CdCl_2$ (14.9 mmol) and 22 ml of anhydrous ether. This addition was carried out such that no ebullition occurred. The solution was then stirred at room temperature for 20–30 min before the Gilman test was performed. In all cases the test was negative before the reaction was allowed to proceed to the next step.

The dimethylcadmium reagent was cooled in an ice–salt bath to an internal temperature of 0°; 2 g of 2-phenylpropanal (14.9 mmol) dissolved in 10 ml of anhydrous ether was added at such a rate that the internal temperature did not exceed 5°. The solution was stirred for 15 min after the addition was complete at the ice–salt bath temperature. The bath was subsequently removed and the solution stirred at ambient temperature for an additional 105 min.

The solution was then cooled in an ice–salt bath and hydrolyzed with 30 ml of saturated $NaHCO_3$ solution at such a rate that the internal temperature did not exceed 10°. The layers were separated, the aqueous layer being extracted twice with ether. The ether layers were combined, dried over $MgSO_4$, and concentrated on a rotary evaporator at 25° or below, yielding 2.1 g of crude product. Glpc analysis of the crude product was carried out on FFAP as above.

Reaction of *in Situ* Dimethylzinc (Br, Br) with 2-Phenylpropanal.—The procedure followed was essentially that described for the reactions of *in situ* cadmium reagents. Glpc analysis of the crude reaction mixtures indicated that, in some instances a considerable amount of zinc salt was carried through the work-up procedure, as evidenced by the presence of variable amounts of olefin in addition to the expected threo and erythro alcohols. The per cent olefin increased unless the injector port of the chromatograph was cleaned regularly. The nmr spectrum gave no evidence of olefin in the samples prior to injection.

In cases where the presence of zinc salt was suspected, the crude product was taken up in benzene and a small amount of petroleum ether added until the solution became cloudy. The flask was cooled to 0° and allowed to stand for several minutes. Generally, a quantity of zinc salt settled out, and additional amounts of petroleum ether were added until no more solid separated. The salts were removed by filtration, the solution concentrated on a rotary evaporator, and the residue analyzed by glpc as outlined above. Values denoting the relative amounts of threo and erythro alcohols (Table II) were reproducible within ±1% and those of unchanged aldehyde within ±5% in separate reaction runs.

Control Experiment.—The individual *threo*- and *erythro*-3-phenyl-2-butanols were mixed with 1 molar equiv of 2-phenylpropanal and 2 molar equiv of dimethylzinc or dimethylcadmium under conditions similar to those described for the reaction of the *in situ* reagents. After hydrolysis and work-up, percentages obtained by glpc indicated no equilibration of diastereomers.

Preparation of 2-Phenyl-1-propanol.—Lithium aluminum hydride reduction of 2-phenylpropanal afforded 2-phenyl-1-propanol, which had a longer retention time on FFAP than either of the diastereomeric addition alcohols (4a and 4b).

Preparation of 3-Phenyl-2-butanone.—Preparation of 3-phenyl-2-butanone was accomplished by CrO_3 oxidation in acetone solution of a crude mixture of the butanols obtained by the reaction of 2-phenyl-propanal with MeMgI. The ketone was not isolated from the reaction mixture, but the reaction was followed by nmr and glpc. The latter indicated that the ketone had a retention time on FFAP slightly longer than that of 2-phenylpropanal. For all experiments with dimethylcadmium and 2-phenylpropanal, 3-phenyl-2-butanone and 2-phenylbutanol (reduction product) constituted no more than 3% of the total product.

Registry No.—**1**, 93-53-8; **2**, 2439-43-2; **3**, 2439-44-3; 3-methyl-2-phenylbutanoic acid, 3508-94-9; methylmagnesium iodide, 917-64-6; methylmagnesium bromide, 75-16-1; dimethylcadmium, 506-82-1; methylcadmium bromide, 25837-91-6; methylcadmium iodide, 25837-90-5; dimethylzinc, 544-97-8; methylzinc iodide, 18815-73-1; methylzinc bromide, 18815-74-2.

(19) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 98 ff; (b) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, pp 126, 127.

Synthetic Reactions by Complex Catalysts. XIX. Copper-Catalyzed Cycloaddition Reactions of Isocyanides. Novel Synthesis of Δ^1-Pyrroline and Δ^2-Oxazoline

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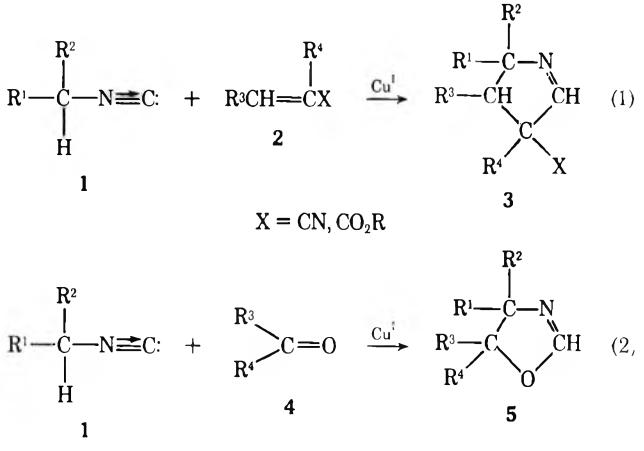
Isonitriles having an acidic hydrogen at the α-carbon atom such as benzyl isocyanide and carbethoxymethyl isocyanide have been found to react with the carbon–carbon double bond of α,β-unsaturated nitriles and carbonyl compounds in the presence of Cu_2O catalyst to produce Δ^1- (or Δ^2-) pyrroline derivatives in high yields. With Cu_2O catalyst, these isocyanides reacted also with the carbon–oxygen double bond of the carbonyl compound to produce Δ^2-oxazoline derivatives. Because of the high selectivity of the reaction in high yields, these two cycloaddition reactions are conveniently employed for synthetic purposes. Reaction schemes have been presented for these two reactions. An organocopper–isonitrile complex is first formed by the abstraction of the hydrogen of isonitrile by Cu_2O, and the organocopper complex adds to the C=C double bond and to the C=O double bond, respectively. The copper organic species thus formed react with the isonitrile group at the γ position to accomplish the ring closure.

For some years, we have been exploring the catalytic activity of copper–isocyanide complexes and have found several versatile reactions.[1-4] This paper describes novel and useful cycloaddition reactions of isocyanides containing acidic α hydrogen to the carbon–carbon double bonds of α,β-unsaturated carbonyl and nitrile compounds 2 (eq 1) and with the carbon–oxygen double bonds of carbonyl compound 4 (eq 2).

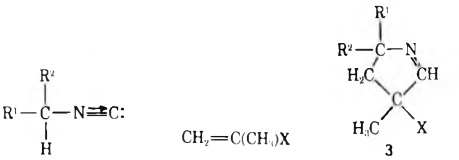


The reactions catalyzed by copper–isocyanide complexes, which have been hitherto found by us, are the dimerization of α,β-unsaturated carbonyl and nitrile compounds[2-4] and Michael addition reactions.[5] In the mechanistic scheme of the dimerization reaction,[3,4] an organocopper–isocyanide complex is first formed from the polar olefin and copper–isocyanide complex, and the addition of the organocopper complex to the second molecule of olefin is the essential step. In Michael addition reaction,[5] an organic complex of copper having an isocyanide ligand is formed from the acidic hydrogen component and copper–isocyanide complex, and the organic complex of copper–isocyanide then adds to the olefin. In both cases, isocyanide serves as a necessary ligand of the catalyst complex, but it is not incorporated into the products. The isocyanide component of the cycloaddition of the present study, however, has an acidic hydrogen and it is incorporated into the product. It assumes also the role of the essential ligand of the catalyst.

Reaction of Isocyanide with α,β-Unsaturated Carbonyl and Nitrile Compounds.—The results of the reaction of isocyanide having an active α hydrogen with α,β-unsaturated carbonyl and nitrile compounds by means of copper catalyst are shown in Tables I and II. Table I shows the results of the reactions with methacrylonitrile and methyl methacrylate. The products **3** are derivatives of Δ^1-pyrroline, and product yields are fairly high. (Identification data of the products are summarized in Table IV.) The products were obtained as mixtures of the two isomers due to the 3-C and 5-C configurations in **3**. Some of these isomer

TABLE I

Cu_2O-CATALYZED REACTION OF ISOCYANIDE WITH α-METHYL α,β-UNSATURATED ESTERS AND NITRILES[a]



R^1	R^2	X	3 Yield, %	Isomer ratio[b]
Ph	H	CN	**3a**, 70	1.0/1.0[c]
		CO_2CH_3	**3b**, 94	1.0/1.0[d]
Ph	CH_3	CO_2CH_3	**3c**, 95	0.85/1.0[c]
		CN	**3d**, 85	1.0/1.0[c]
CO_2Et	H	CO_2CH_3	**3e**, 85	1.5/1.0[d]
		CN	**3f**, 31	0.4/1.0[d]

[a] A mixture of isocyanide (10 mmol), olefin (10 mmol), and Cu_2O (0.20 mmol) in benzene (3 ml) was heated under nitrogen at 80° for 3 hr. [b] The ratio of two configurational isomers due to C-3 and C-5 configuration. [c] Isomer ratio based on glpc and nmr analyses. [d] Isomers were not separated, and the ratios were based on nmr.

(1) (a) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and H. Yoshioka, *Tetrahedron Lett.*, 6121 (1966); *Bull. Chem. Soc. Jap.*, **42**, 3310 (1969); (b) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and N. Takeda, *Tetrahedron Lett.*, 521, 1273 (1967); *Can. J. Chem.*, **47**, 1217 (1969); (c) T. Saegusa Y. Ito, and S. Kobayashi, *Tetrahedron Lett.*, 935 (1968); (d) T. Saegusa, S. Kobayashi, Y. Ito, K. Hirota, and Y. Okumura, *Bull. Chem. Soc. Jap.*, **41**, 1638 (1968); (e) T. Saegusa, Y. Ito, S. Kobayashi, and K. Hirota, *J. Amer. Chem. Soc.*, **89**, 2240 (1967).

(2) T. Saegusa, Y. Ito, S. Kobayashi, and S. Tomita, *Chem. Commun.*, 273 (1968).

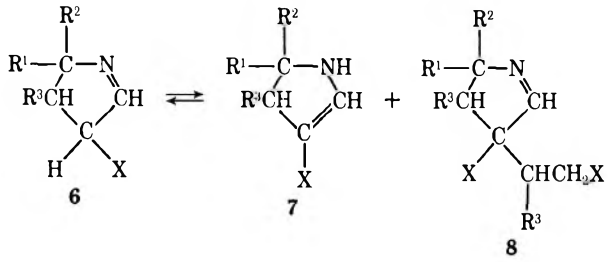
(3) T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *J. Org. Chem.*, **35**, 670 (1970).

(4) T. Saegusa, Y. Ito, H. Kinoshita, and S. Tomita, *Bull. Chem. Soc. Jap.*, **43**, 877 (1970).

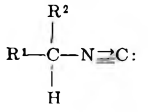
(5) T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, unpublished work.

TABLE II

Cu_2O-CATALYZED REACTION OF ISOCYANIDE WITH α-UNSUBSTITUTED α,β-UNSATURATED ESTERS AND NITRILES[a]



6 7 8

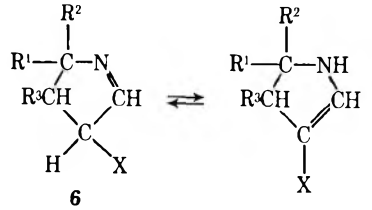


R^1	R^2	$R^3CH{=}CHX$ R^3	X (mmol)	Yield, % (6 + 7)	Tautomer ratio,[b] 6/7	Yield, % (8)
Ph	H	H	CO_2Me (20)	(6a + 7a) 5		8a, 75
Ph	Me	H	CO_2Me (20)	(6b + 7b) 2~3	Mostly 6	8b, 80
		H	CO_2Me (10)	(6b + 7b) 22	Mostly 6	8b, 39
		CH_3	CO_2Me (10)	(6c + 7c) 60	2/1	c
		CO_2Me	CO_2Me (20)	(6d + 7d) 28	4/5	c
CO_2Et	H	H	CO_2Me (20)	(6e + 7e) 19	1/3	8e, 70
		H	CO_2Me (10)	(6e + 7e) 57		8e, 2~3
		CH_3	CO_2Me (10)	(6f + 7f) 30	1/4	c
		H	CN (10)	(6g + 7g) 37	Trace/1	c
		CO_2Me	CO_2Me (20)	(6h + 7h) 75	1/8	c

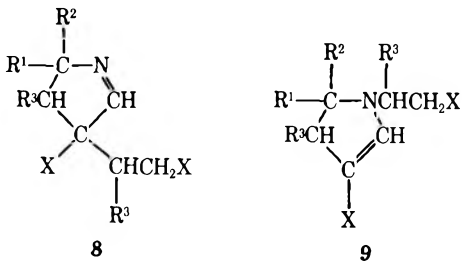
[a] A mixture of isocyanide (10 mmol), olefin, and Cu_2O (0.20 mmol) in benzene (3 ml) was heated under nitrogen at 80° for 3 hr. [b] The tautomer ratio was determined by nmr analysis. [c] Could not be isolated by distillation.

mixtures were separated by preparative glpc. The comparison of the nmr spectra of two isomers clearly indicates that they are configurational isomers.

The results of the reaction with α-unsubstituted α,β-unsaturated carbonyl and nitrile compounds are given in Table II, in which two kinds of products were obtained. The first one is a tautomeric mixture of Δ^1- and Δ^2-pyrroline derivatives (**6** and **7**) due to the migration of the 3-C hydrogen of **6**. The second one consists of 1 mol of isocyanide and 2 mol of olefin. The second product, shown to be **8**, arises by the secondary Michael addition of **6** (or **7**) to the second molecule of olefin. This was confirmed by a reference experiment in which **8e** ($R^1 = CO_2Et$; $R^2 = H$; $R^3 = H$; and $X = CO_2CH_3$) was produced in Michael addition of **6e** (= **7e**) with methyl acrylate in the presence of the Cu_2O–isocyanide catalyst. The alternative species **9** was not isolated. The relative ratio of the amounts of the products, **6** (or **7**)/**8** is controlled by the olefin/isocyanide ratio of the initial feed of the reaction. As expected, the production of **8** is favored when the olefin/isocyanide ratio is increased.



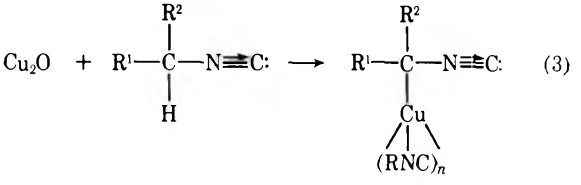
6 7



8 9

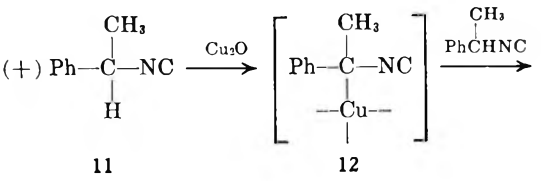
For the cycloaddition reactions in Tables I and II, Cu_2O was the most active among metal salts and oxides so far as examined. Copper(II) acetylacetonate and CuO showed considerable activity. Other copper compounds such as cupric and cuprous halides or acetate were inactive. Moreover, oxides of Ag, Fe(II), and Hg(II) were also inactive.

The key intermediate of the cycloaddition reaction is assumed to be an organocopper–isocyanide complex **10**, which is formed from isocyanide and Cu_2O. The α-acidic hydrogen is replaced by copper(I) having the ligand of other isocyanide molecules (eq 3). The isocyano group of the parent isocyanide whose acidic hydrogen has been replaced by copper may also coordinate to another copper. The formation of an intermediate organocopper–isocyanide complex **10** is supported by the finding that optically active α-phenylethyl isocyanide (**11**) is racemized readily at room temperature by Cu_2O (eq 4). It is reasonable to assume that racemization takes place by inversion of the carbanion of the organocopper–isocyanide complex **12**. Furthermore, the racemization rate of para-substituted phenylethyl isocyanide was dependent upon the nature of the substituent. The order of the racemization rate was p-Cl > H > p-MeO. This order is consistent with the assumption that the α-acidic hydrogen of phenyl-

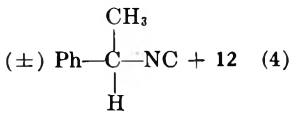


(3)

10



11 12

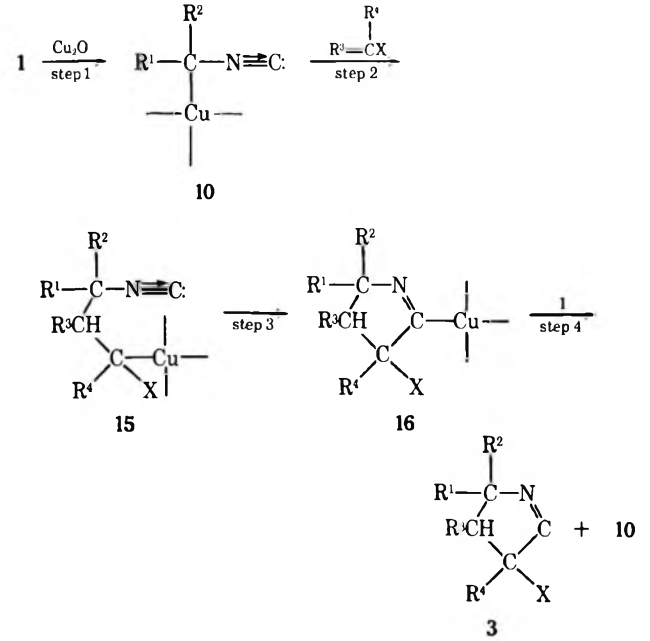


13

ethyl isocyanide is removed as proton to form an organocopper complex **12**. An organocopper–isocyanide complex has been assumed as the key intermediate in the reactions catalyzed by the copper–isocyanide complexes, *i.e.*, dimerization of α,β-unsaturated carbonyl and nitrile compounds[2-4] and in Michael addition reaction.[5] Especially the cyclopentadienyl-copperisocyanide complex **14**, which has been assumed in the Michael addition reaction of the cyclopentadiene homologs, was prepared and isolated from cyclopentadiene, *tert*-butyl isocyanide, and Cu_2O[6] [$(C_5H_5)Cu(I)$-(CN-*tert*-Bu) (**14**)].

Scheme I, including the organocopper–isocyanide intermediate, may be presented for the copper-catalyzed

SCHEME I



10

15 **16**

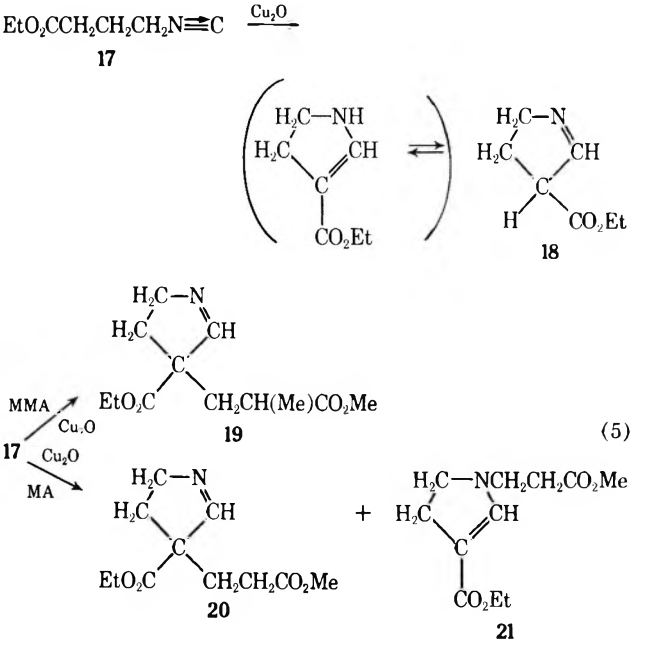
3

cycloaddition of isocyanide with olefin. The organocopper–isocyanide complex **10** adds to the polar olefin to produce an intermediate **15**. In the complex **15**, a cyclization between the isocyanide group and the alkyl copper linkage gives rise to **16** (step 3), and the abstraction of a proton by **16** from the second molecule of **1** produces the final product **3** and **10** (step 4). From **10** thus produced, the second reaction cycle is initiated.

Step 3 is worthy of particular attention; *i.e.*, the isocyanide group may have possibly been activated by coordination to another copper. An alternative reaction proceeding *via* the complex **15** has been realized, in which γ-carbethoxypropyl isocyanide **17** was cyclized by the

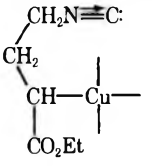
(6) T. Saegusa, Y. Ito, and S. Tomita, *J. Amer. Chem. Soc.*, in press.

treatment with Cu_2O. A tautomer mixture of 3-carbethoxy-Δ^1- and -Δ^2-pyrroline (**18**) was isolated in a yield of 19%. Further, when this reaction was carried out in the presence of methyl methacrylate (MMA) or methyl acrylate (MA), Δ^1- or Δ^2-pyrroline derivatives of **19**–**21**, which was regarded as secondary Michael addition products of **18** with MMA or with MA, were isolated in fairly good yields (eq 5). The hydrogen on the



17 **18** **19** **20** **21** (5)

γ-carbon atom of **17** has an acidic character due to the carbethoxy group which is replaced by copper to produce organocopper complex **22**. The cyclization of the complex **22** is the same elementary reaction of step 3 in Scheme I. In the cyclization of **22**, the isocyanide group may have been coordinated to another copper.



22

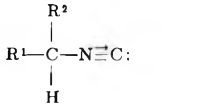
The cyclization of **17** to **18** by copper catalyst is formally an insertion of the isocyanide group into the carbon–hydrogen bond. A series of copper-catalyzed insertion reactions of isocyanide have been found by us. The insertions of isocyanide into the N–H bond of amine,[1a] O–H bond of alcohol,[1b] P–H bond of phosphine,[1c] S–H bond of thiol,[1d] and Si–H bond of silane[1e] constitute a general reaction of "formimidation." The cyclization of **17** is an "intramolecular formimidation" and affords a significant extension of the isocyanide insertion. The isocyanide insertion into the carbo–hydrogen bond is possible only when the isocyanide group and active hydrogen are appropriately situated in a single molecule. The reaction between ethyl propionate and cyclohexyl isocyanide with Cu_2O catalyst did not occur. In addition, β-carbethoxyethyl isocyanide in which an acidic hydrogen is at the β position from the isocyanide group was not cyclized under the same conditions with Cu_2O catalyst.

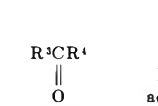
Reaction of Isocyanides with Carbonyl Compounds.— The results of the reaction of isocyanide having an ac-

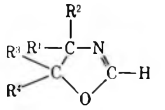
tive hydrogen with the carbon–oxygen double bond of carbonyl compounds by means of copper catalyst are shown in Table III. The structure of the products

TABLE III

Cu_2O-CATALYZED REACTION OF ISOCYANIDE WITH CARBONYL COMPOUNDS[a]







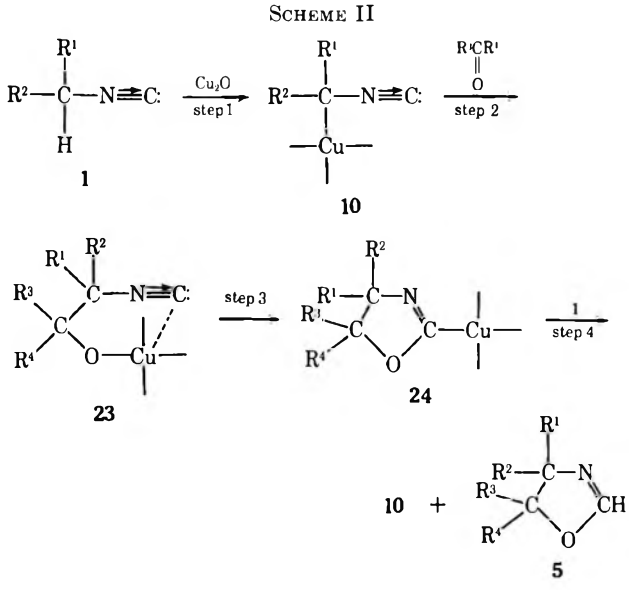
(10 mmol)		(20 mmol)		Reaction time,	5	Isomer
R^1	R^2	R^3	R^4	hr	Yield, %	ratio
Ph	H	Me	Me	3	**5a**, 60	
Ph	H	Ph	Me	3	**5b**, 75[b]	1.5/1.0[b]
Ph	H	$-(CH_2)_4-$		15	**5c**, 82	
Ph	H	*i*-Pr	H	1	**5d**, 85[b]	*d*
Ph	Me	Et	Me	15	**5e**, 41[b]	0.6/1.0[c]
CO_2Et	H	Ph	Me	3	**5f**, 75[b]	1.0/1.0[b]
CO_2Et	H	*i*-Pr	H	1	**5g**, 73[b]	*d*
CO_2Et	H	$-(CH_2)_4-$		15	**5h**, 57	

[a] A mixture of isocyanide (10 mmol), carbonyl compound (20 mmol), and Cu_2O (0.20 mmol) in benzene was heated under nitrogen at 80° for the indicated time. [b] Isomer ratio was determined by glpc. [c] Isomer ratio was determined by nmr. [d] Isomer ratio could not be determined.

of Δ^2-oxazoline derivatives were convincingly determined by ir and nmr spectra as well as elemental analysis. Except for the oxazoline obtained from benzyl isocyanide and acetone, all the products are mixtures of the configurational isomers due to the 4-C and 5-C configurations.

Scheme II may be presented to explain the isocyanide–carbonyl reaction, in which the organocopper–isocyanide complex **10** is a key intermediate as in the isocyanide polar olefin reaction. The addition of **10** to the carbonyl group produces a copper alkoxide complex **23** (step 2), and the intramolecular reaction between the copper alkoxide and isocyanide groups in **23** is a cyclization process (step 3). The copper complex of the cyclized species **24** will abstract a hydrogen from the second molecule of **1** to afford the product of the Δ^2-oxazoline derivative and **10** (step 4). The reaction cycle is repeated from **10**.

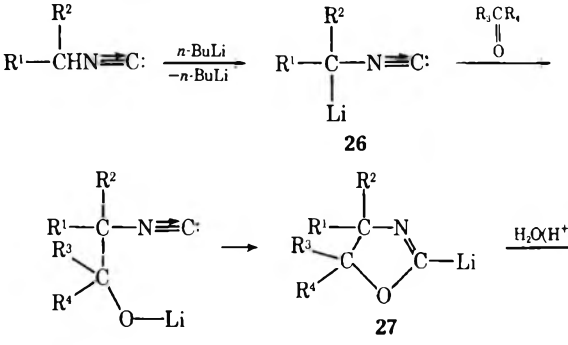
SCHEME II



Step 3 is regarded as the insertion of isocyanide into the copper–oxygen bond. This process may be taken to correspond to the copper-catalyzed reaction of isocyanide with alcohol[1b] in which the copper alkoxide–isocyanide complex **25** from Cu_2O, alcohol, and isocyanide plays an important role.

$$ROH + Cu_2O + R'NC \longrightarrow \underset{\mathbf{25}}{ROCu(R'NC)_n}$$

The copper-catalyzed cycloaddition of isocyanides with carbonyl compounds is interestingly compared with the base-induced reaction of the same pattern. Schöllkopf, *et al.*,[7,8] reported two procedures. One was performed by means of alkyllithium. Alkyllithium abstracts the α hydrogen of isocyanide to give the α-lithio isocyanide **26** whose addition to the carbonyl compound followed by cyclization forms the lithio compound of oxazoline **27**. By this procedure, the usual alkyl isocyanides were allowed to react with carbonyl compounds. The second procedure was due to the use



of the NaCN–EtOH system, which was applied only to carbethoxymethyl isocyanide. The reactions proceed catalytically in this case. Comparison between the copper-catalyzed cycloaddition and the usual base-catalyzed one is the subject of future studies.

Experimental Section

Reagents.—Benzyl isocyanide, α-phenylethyl isocyanide, and carbethoxymethyl isocyanide were prepared by Ugi's procedure using phosgene.[9] Cyclohexyl isocyanide was prepared by a method using phosphorus oxychloride.[10]

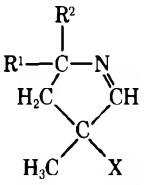
Reaction of Isocyanides with α-Methyl α,β-Unsaturated Carbonyl and Nitrile Compounds.—A mixture of isocyanide (10 mmol), olefin (20 mmol), and Cu_2O (0.2 mmol) in 3 ml of benzene was heated at 80° for 3 hr. The product was isolated by fractional distillation. The olefins employed were methyl methacrylate and methacrylonitrile. The products were a mixture of two configurational isomers. Some of these isomers were separated by glpc. The identifications are summarized in Table IV.

Reaction of Isocyanides with α,β-Unsaturated α-Unsubstituted Carbonyl and Nitrile Compounds.—The reactions were carried out under the same conditions as above. In the reactions of methyl acrylate with $PhCH_2NC$, with PhCH(Me)NC, and with EtO_2CCH_2NC, the glpc analysis of the reaction mixture showed two peaks, A and B, of products. The retention time of A was shorter than that of B. Analysis of the isolated sample showed that fraction A contains Δ^1- and Δ^1-pyrroline derivatives **6** and **7** and fraction B was the Michael adduct **8** of **6** with methyl acrylate. In the reactions of other olefins shown in Table II, only one glpc peak was observed, which corresponded to a tautomeric mixture of **6** and **7**. The identification data of the products are summarized in Table V.

(7) F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 6231 (1968).
(8) D. Hoppe and U. Schöllkopf, *Angew. Chem.*, **80**, 290 (1970).
(9) I. Ugi, U. Fetzer, H. Knupfer, and K. Offermann, *ibid.*, **77**, 492 (1965).
(10) I. Ugi and R. Meyer, *Ber.*, **93**, 239 (1960).

TABLE IV

PRODUCTS FROM ISOCYANIDES AND α-METHYL α,β-UNSATURATED CARBONYL AND NITRILE COMPOUNDS[a]



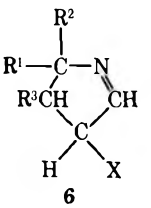
3

Compd	R^1	R^2	X	Bp, °C (mm)	Calcd (found) C, %	H, %	N, %	Principal ir bands, cm^{-1}	Nmr, τ (in $CDCl_3$)	Isomer ratio
3a	Ph	H	CN	104–105 (2)	78.23 (78.18)	6.57 (6.66)	15.21 (14.94)	1615 (w), 2215 (w)	8.48 (s, CH_3), 7.80 and 7.46 (2 q, CH_2), 4.76 (t, each was d, ≥CH), 2.71 (s, Ph), 2.46 (d, N=CH)[a] 8.45 (s, CH_3), 8.27 and 7.02 (2 q, CH_2), 4.62 (t, each was d ≥CH), 2.71 (s, Ph), 2.51 (d, N=CH)[a]	1/1
3b	Ph	H	CO_2Me	101–102 (2)	71.86 (72.02)	6.96 (7.12)	6.45 (6.38)	1618 (w), 1724 (s)	8.59 and 8.56 (2 s, CH_3), 8.60–6.80 (m, CH_2), 6.32 and 6.31 (2 s, CO_2CH_3), 4.82 and 4.71 (2 t, each was d ≥CH), 2.78 (s, Ph), 2.48 and 2.38 (2 d, N=CH). A set of absorptions due to isomers are equal intensity	1/1
3c	Ph	CH_3	CO_2Me	86–88 (0.1)	72.70 (72.74)	7.41 (7.33)	6.06 (6.03)	1625 (w), 1732 (s)	8.49 and 8.36 (2 s, CH_3), 8.00 and 7.25 (2 d, CH_2), 6.42 (s, CO_2CH_3), 2.71 (s, Ph), 2.49 (s, N=CH)[a] 8.70 and 8.44 (2 s, CH_3), 8.00 and 7.25 (2 d, CH_2), 6.22 (s, CO_2CH_3), 2.71 (s, Ph), 2.49 (s, N=CH)[a]	0.85/1.0
3d	Ph	CH_3	CN	107–110 (0.7)	78.75 (78.66)	7.12 (7.11)	14.13 (14.02)	2226 (w), 1628 (w)	8.60 and 8.37 (2 s, CH_3), 7.89 and 7.25 (2 d, CH_2), 2.70 (s, Ph), 2.60 (s, N=CH)[a] 8.60 and 8.77 (2 s, CH_3), 7.89 and 7.25 (2 d, CH_2), 2.70 (s, Ph), 2.60 (s, N=CH)[a]	1/1
3e	CO_2Et	H	CO_2Me	85–87 (1)	56.32 (56.11)	7.09 (7.11)	6.57 (6.51)	1620 (w), 1720 (s)	8.66 (t, CH_3CH_2), 8.56 (minor) and 8.50 (major) (2 s, CH_3), 8.25–7.00 (m, CH_2), 6.22 (s, CO_2CH_3), 5.73 (q, CH_3CH_2), 5.15 (t, each of t was d, ≥CH), 2.46 (major) and 2.37 (minor) (2 d, N=CH)[b]	1.5/1.0
3f	CO_2Et	H	CN	112–113 (5)	59.98 (59.45)	6.71 (6.85)	15.55 (15.30)	1627 (w), 1720 (s), 2222 (w)	8.67 (minor) and 8.59 (major) (2 t, CH_3CH_2), 8.47 (s, CH_3), 8.20–7.00 (m, CH_2), 5.60 (q, CH_3CH_2), 5.10 (t, each of t was d, ≥CH), 2.45 (major) and 2.39 (minor) (2 d, N=CH)[b]	0.4/1.0

[a] Each of two configurational isomers was isolated by glpc. Their nmr absorptions are given here separately. Isomer ratio was calculated from glpc peaks and from the intensity ratio of the corresponding isomer absorptions by nmr of the isomer mixture. [b] Two isomers were not separated by glpc. Nmr data of a mixture of two isomers are given here. Isomer ratio was calculated from the nmr intensity ratio of the corresponding isomer absorptions.

TABLE V

PRODUCTS FROM ISOCYANIDES AND α-UNSUBSTITUTED α,β-UNSATURATED CARBONYL AND NITRILE COMPOUNDS



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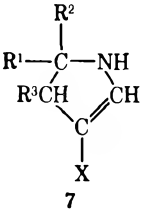

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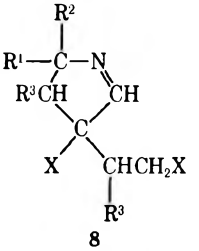


8

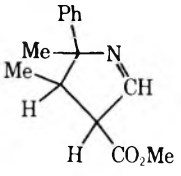
Compd, major (minor)	R^1	R^2	R^3	X	Bp, °C (mm)	Calcd (found) C, %	H, %	N, %	Principal ir bands, cm^{-1}	Nmr, τ (in $CDCl_3$)[a]	Tautomer ratio[b]
6a (**7a**)	Ph	H	H	CO_2Me	Preparative glpc				1595 (s), 1675 (s), 1730 (s), 3310 (s)		
8a	Ph	H	H	CO_2Me	161–163 (0.1)	66.42 (66.17)	6.62 (6.74)	4.84 (4.98)	1615 (w), 1726 (s)	8.00–7.50 (m, CH_2), 6.33, 6.29 (2 s, CO_2CH_3), 4.83 (t, each of t was d, ≥CH), 2.72 (s, Ph), and 2.37 (d, N=CH)	No isomer from nmr

TABLE V
(*Continued*)

Compd, major (minor)	R¹	R²	R³	X	Bp, °C (mm)	Calcd (found) C, %	H, %	N, %	Principal ir bands, cm⁻¹	Nmr, τ (in $CDCl_3$)[a]	Tautomer ratio[b]
6b (7b)	Ph	Me	H	CO_2Me	Preparative glpc 150–170 (0.1)				1595 (w), 1625 (m), 1730 (s), 3300 (m)	8.34 (s, CH_3, 3 H), 7.60 (d, CH_2, 2 H), 6.32 (s, CO_2CH_3, 3 H), 6.2–6.5 (m, ⩾CH, 1 H), 2.4–2.8 (m, Ph and N=CH, 6 H), >NH absorption could not be detected	Almost exclusively **6b**[c]
8b	Ph	Me	H	CO_2Me		67.31 (67.68)	6.98 (7.26)	4.62 (4.65)	1625 (w), 1730 (s)	8.46, 8.34 (equal intensity) (2 s, CH_3), 8.70–7.10 (m, CH_2), 6.46, 6.40, 6.31, 6.24 (equal intensity) (4 s, CO_2Me), 2.76 (s, Ph), and 2.76, 2.50 (equal intensity) (2 s, N=CH)	1/1 configurational isomer
6c (7c)	Ph	Me	CH_3	CO_2Me	143–145 (0.9)	72.10 (72.55)	7.41 (7.50)	6.06 (5.90)	1595 (m), 1660 (s), 1740 (s), 3310 (s)	9.41 (d, ⩾$CHCH_3$, **6** isomer, 2 H), 8.88 (d, >$CHCH_3$, **7** isomer, 1 H), 8.50, 8.42, 8.25 (*ca.* equal intensity) (3 s, $PhCCH_3$, 3 H), 7.0–8.0 (m, ⩾CH, 5/9 H), 6.43 6.30, 6.20, 6.10 (4 s, CO_2CH_3, 3 H), 5.46 (broad s, NH, 1/9 H), and 2.4–3.0 (m, Ph, CH=CN<, HC=N, 6 H)	**6c**/**7c** = 2/1
7d (6d)	Ph	Me	CO_2Me	CO_2Me	150–155 (0.5)	65.44 (65.75)	6.22 (6.33)	5.09 (5.15)	1590 (m), 1662 (s), 1720 (s), 3310 (s)	8.56–7.86 (6 s, CH_3, 3 H), 7.60 (⩾CH, **7** isomer 5/9 H), 6.85 (d, ⩾CH, **6** isomer 8/9 H), 6.0–6.4 (6 s, CO_2CH_3, 6 H), 4.6–5.2 (broad s, NH, **7** isomer 5/9 H), 2.3–2.9 (m, Ph NCH=, N=CH, 6 H)	**6d**/**7d** = 4/5
7e (6e)	CO_2Et	H	H	CO_2Me	128–130 (0.7)	54.26 (54.39)	6.85 (6.59)	7.03 (6.93)	1590 (m), 1660 (s), 1725 (s), 3310 (s)	8.66 (t, CH_3CH_2, 3 H), 7.8–6.7 (m, CH_2, ⩾CH, 3 H), 6.28 (s, CO_2Me, 3 H), 5.75 (q, CH_3CH_2, 2 H), 5.0–5.5 (broad s, >NH, 3/4 H), 2.75 (m, >C=CH, 3/4 H), 2.30 (m, N=CH, 1/4 H)	**6e**/**7e** = 1/3
8e	CO_2Et	H	H	CO_2Me	133–134 (0.7)	54.73 (54.67)	6.71 (6.86)	4.91 (4.96)	1619 (w), 1729 (s)	8.70 (t, CH_3CH_2), 8.00–7.00 (m, CH_2), 6.25, 6.23 (2 s, CO_2Me), 5.75 (q, CH_3CH_2), and 2.32 (broad s, N=CH)	
7f (6f)	CO_2Et	H	CH_3	CO_2Me	120–122 (4)	56.32 (56.18)	7.09 (7.04)	6.57 (6.28)	1590 (m), 1662 (s), 1727 (s), 3350 (s)	8.50–8.95 (overlap of t for isomer, CH_2CH_3 and d for CH_3CH<, 6 H), 7.8–7.1 (m, CH_3CH<, 1 H), 6.8–6.4 (q, EtO_2CCH<, 1 H), 6.28 (s, major peak), 5.96–6.26 (4 s, minor peak) (CO_2CH_3, total 3 H), 5.4–5.96 (overlap q, CH_2CH_3, 2 H), 5.1 broad s, >NH, 4/5 H), 2.73 (d, NHCH=C<, 4/5 H), and 2.20 (m, >N=CH, 1/5 H)	**6f**/**7f** = 1/4
7g (6g)	CO_2Et	H	H	CN	128–130 (0.4)	57.82 (57.75)	6.07 (6.19)	16.86 (16.97)	1595 (m), 1731 (s), 2195 (w), 3355 (s)	8.69 (t, CH_3CH_2, 3 H), 6.96 (d, CH_2, 2 H), 5.75 (q, CH_3CH_2, 2 H), 5.56 (t, ⩾CH, 1 H), 4.82 (s, >NH, 1 H), 2.99 (m, >C=CH, 1 H), and 2.40 (m, N=CH, trace)	Almost **7g**[d]
7h (6h)	CO_2Et	H	CO_2Me	CO_2Me	164–165 (1)	51.36 (50.96)	5.88 (5.90)	5.45 (5.23)	1590 (m), 1670 (s), 1730 (s), 3345 (s)	8.70 (t, CH_3CH_2, 3 H), 6.31, 6.21 (2 s, CO_2Me, 6 H), 5.76 (q, CH_3CH_2, 2 H), 5.34 (d, >$CHCO_2Me$, 1 H), 4.75 (s, >NH, 8/9 H), 2.68 (m, >C=CH, 8/9 H), and 2.35 (m, N=CH, 1/9 H)	**6h**/**7h** = 1/8

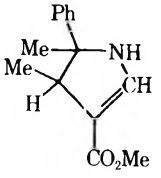
[a] Nmr absorption for a mixture of **6** and **7** isomers. [b] Tautomer ratio of **6**/**7** was calculated from the intensity ratio of >NH absorption and from the intensity ratio of N=CH/>C=CHNH absorptions. Configurational isomer ratio of **8b** was calculated from the PhCMe intensity ratio of each isomer. [c] The tautomer is present mostly as **6b** from nmr, but the ir spectrum shows the presence a small amount of **7b** by ν_{NH} absorption. [d] Ir and nmr spectra show that the tautomer is present almost as **7g**, but a weak N=CH group in the nmr spectrum shows the presence a small amount of **6g**.

The constituent parts of the peak A fraction were examined by nmr and ir spectra. For example, the ir spectrum of the reaction product (6c–7c) of PhCH(Me)NC with metyl crotonate showed four characteristic absorptions at 3310 (s, ν_{NH} of 7c), 1740 (s, $\nu_{C=O}$ of 6c), 1660 (s, $\nu_{C=O}$ of 7c), and 1595 cm^{-1} (m, $\nu_{C=C}$ of 7c). An expected absorption of $\nu_{C=N}$ of 6c was included in the strong absorption at 1660 cm^{-1}. The nmr spectrum of 6c–7c was as follows: τ 9.41 (d, 2 H) and 8.88 (d, 1 H, both were >CHC**H**$_3$), 8.50, 8.42, and 8.25 (three singlets of equal intensity, PhCC**H**$_3$, total 3 H), 7.0–8.0 (m, ≥CH, $^5/_3$ H), 6.43–6.10 (four singlets, CO_2CH_3, total 3 H), 5.46 (broad s, >NH, $^1/_3$ H), and 2.4–3.0 (m, C_6H_5, CH=CN<, CH=N, 6 H). The peak at τ 5.46 disappeared by D_2O treatment. In other cases, the analysis of the peak A fraction gave the same conclusion, *i.e.*, it consists of 6 and 7. These nmr spectrum fitted a mixture of 6c and 7c.



6c

four configurational isomers



7c

two configurational isomers

The formation of four isomers of these six isomers was suggested by the four singlets of CO_2CH_3 in the case of 6c–7c. The nmr spectrum of 6d–7d showed the formation of all six isomers.

In addition, the doublet or multiplet peaks of NHC**H**=C< of 7e (6e) and 7h (6h) were decoupled and became singlets by D_2O treatment. This observation supports the above conclusion.

The composition of 6c–7c was given by nmr; *i.e.*, the intensity of >NH was $^1/_3$ H, and, thus, 6c/7c = 2/1. In accordance with this value, the intensity ratio of >CHC**H**$_3$ absorptions at τ 9.41 and 8.88 was 2/1.

Preparation of γ-Carbethoxypropyl Isocyanide and β-Carbethoxyethyl Isocyanide.—To a solution of 10 ml of ammonia in 450 ml of chloroform 120 g of the HCl salt of ethyl γ-aminobutyrate was added. The mixture was stirred at 0° for 10 min. The chloroform solution was filtered in order to remove ammonium chloride; to this filtrate 150 ml of ethyl formate was added and the mixture refluxed for 24 hr. *N*-(γ-Carbethoxypropyl)formamide was distilled at 146° (0.7 mm). From *N*-(γ-carbethoxypropyl)formamide, γ-carbethoxypropyl isocyanide [bp 82–83° (4 mm)] was prepared according to the phosgene method.[9] β-Carbethoxyethyl isocyanide [bp 60–62° (0.9 mm)] was prepared by the same procedure.[9]

Cyclization of γ-Carbethoxypropyl Isocyanide.—A mixture of 1.41 g (10 mmol) of γ-carbethoxypropyl isocyanide and 29 mg (0.20 mmol) of Cu_2O in 3 ml of benzene was heated at 80° for 1 hr. Complete consumption of the isocyanide was shown by glpc analysis. The reaction mixture was subjected to vacuum distillation. The fraction boiling at 50–90° (1 mm) was collected. The major product of this distillate was a tautomer mixture of 3-carbethoxy-Δ^1- and -Δ^2-pyrroline (**18**). From the nmr intensity ratio of the absorptions of >NH, N=CH, and >NC=CH, the tautomer ratio of Δ^1/Δ^2 was shown to be about 4/3. The yield was 19%: nmr (in $CDCl_3$) (**18**) τ 8.72, 8.70 (2 t, C**H**$_3$CH$_2$), 7.85–7.00 (m, CH$_2$), 5.84, 5.82 (2 q, CH$_3$C**H**$_2$), 5.25 (d, >NH, $^3/_7$ H), 2.72 (m, CH=C, $^3/_7$ H), and 2.45 (m, N=CH, $^4/_7$ H); principal ir bands (neat) 3310 (s), 1720, (s), 1670 (s), 1620 (w), and 1591 cm^{-1} (m).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.62; H, 7.91; N, 9.90.

Reaction of γ-Carbethoxypropyl Isocyanide with Methyl Methacrylate.—A mixture of 1.41 g (10 mmol) of γ-carbethoxypropyl isocyanide and 2.00 g (20 mmol) of methyl methacrylate and 29 mg (0.20 mmol) of Cu_2O in 3 ml of benzene was heated at 80° for 3 hr. The product, 3-(β-carbomethoxypropyl)-3-carbethoxy-Δ^1-pyrroline (**19**) was isolated in 61% yield by fractional distillation [bp 99–105° (0.4 mm)] along with a small amount of 1-(β-carbomethoxypropyl)-3-carbethoxy-Δ^2-pyrroline: nmr (in $CDCl_3$) (**19**) τ 8.80 (d, CH$_3$CH<), 8.72, 8.70 (2 t, C**H**$_3$CH$_2$), 8.30–7.30 (m, CH$_2$), 6.37, 6.25 (2 s, CO_2CH_3), 5.92, 5.90 (2 q, CH$_3$C**H**$_2$), and 2.57 (t, N=CH); principal ir bands (neat) 1725 (s) and 1621 cm^{-1} (w).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.65; H, 7.80; N, 6.04.

Reaction of γ-Carbethoxypropyl Isocyanide with Methyl Acrylate.—The reaction was carried out under the same conditions as those of the reaction with methyl methacrylate. From the reaction mixture, two products were isolated by fractional distillation. The first product boiling at 108–109° (0.4 mm) was 3-(β-carbomethoxyethyl)-3-carbethoxy-Δ^1-pyrroline (**20**). The yield was 39%. The second fraction boiling at 150–160° (0.5 mm) was 1-(β-carbomethoxyethyl)-3-carbethoxy-Δ^2-pyrroline (**21**). The yield was 17%.

Identification data of **20**: nmr (in $CDCl_3$) τ 8.72, 8.70 (2 t, C**H**$_3$CH$_2$), 8.50–7.30 (m, CH$_2$), 6.30, 6.25 (2, s, CO_2CH_3), 5.92, 5.90 (2 q, CH$_3$C**H**$_2$), and 2.55 (t, N=CH); principal ir bands (neat) 1612 (w) and 1722 cm^{-1} (s).

Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 57.93; H, 7.70; N, 6.18.

Identification data of **21**: nmr (in $CDCl_3$) τ 8.80 (t, CH$_3$CH$_2$), 7.80–7.20, 6.80–6.50 (m, CH$_2$), 6.33 (s, CO_2CH_3), 5.90 (q, CH$_3$CH$_2$), and 3.10 (m, >C=CH); principal ir bands (neat) 1736 (s), 1673 (s) and 1595 cm^{-1} (m).

Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.11; H, 7.72; N, 6.40.

An Attempt of Cyclization of β-Carbethoxyethyl Isocyanide.—A mixture of 1.27 g (10 mmol) of β-carbethoxyethyl isocyanide and 29 mg (0.2 mmol) of Cu_2O in 3 ml of benzene was heated at 80° for 15 hr. No reaction was observed by glpc analysis.

An Attempt of Reaction of Cyclohexyl Isocyanide with Methyl Propionate.—A mixture of 1.09 g (10 mmol) of cyclohexyl isocyanide, 0.88 g (10 mmol) of methyl propionate, and 29 mg (0.2 mmol) of Cu_2O in 3 ml of benzene was heated at 80° for 16 hr. By glpc analysis it was found that the two reagents of isocyanide and propionate remained unreacted in the reaction mixture.

Michael Addition Reaction of 3-Carbomethoxy-5-carbethoxy-Δ^1- and -Δ^2-pyrroline Tautomer Mixture with Methyl Acrylate.—A tautomer mixture of 3-carbomethoxy-5-carbethoxy-Δ^1-pyrroline and its tautomer (0.40 g, 2 mmol) was allowed to react with methyl acrylate (0.17 g, 2 mmol) in the presence of Cu_2O (6 mg, 0.04 mmol) and cyclohexyl isocyanide (0.22 g, 2 mmol) in benzene (1 ml) at 80° for 3 hr. By comparison of the glpc retention time with the authentic sample, the products were identified. The main product was 3-(β-carbomethoxyethyl)-3-carbomethoxy-5-carbethoxy-Δ^1-pyrroline, and a by-product was 1-(β-carbomethylethyl)-3-carbethoxy-5-carbethoxy-Δ^2-pyrroline. In the absence of Cu_2O, no reaction was observed.

Preparation of Optically Active Isocyanides.—The following three isocyanide were prepared, *i.e.*, α-phenylethyl isocyanide, α-(*p*-chlorophenyl)ethyl isocyanide, and α-(*p*-methoxyphenyl)ethyl isocyanide. α-Phenylethylamine was commercially available, and α-(*p*-chlorophenyl)ethylamine and α-(*p*-methoxyphenyl)ethylamine were prepared according to the Leukert reaction.[11] α-Phenylethylamine and α-(*p*-chlorophenyl)ethylamine were optically resolved by means of *l*-malic acid.[11] Optical resolution of α-(*p*-methoxyphenyl)ethylamine was carried out by means of *l*-tartaric acid. Optically active amines were converted into the corresponding formamide by treatment with ethyl formate, and then the formamide derivatives were employed to prepare optically active isocyanides by the phosgene method:[9] (+)-α-phenylethylamine, $[\alpha]^{15}D$ +38.9° (*c* 3.37, C_6H_6); (+)-α-(*p*-chlorophenyl)ethylamine, $[\alpha]^{15}D$ +25.3° (*c* 4.46, C_6H_6); (+)-α-(*p*-methoxyphenyl)ethylamine, $[\alpha]^{15}D$ +16.7° (*c* 5.96, C_6H_6); (+)-α-phenylethyl isocyanide, $[\alpha]^{15}D$ +24.4° (*c* 8.75, C_6H_6); (+)-α-(*p*-chlorophenyl)ethyl isocyanide, $[\alpha]^{15}D$ +13.5° (c 10.47, C_6H_6), bp 50–53° (0.5 mm); (+)-α-(*p*-methoxyphenyl)ethyl isocyanide, $[\alpha]^{15}D$ +19.6° (*c* 9.71 C_6H_6), bp 90–92° (0.4 mm).

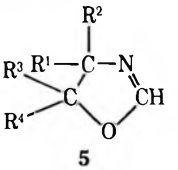
Racemization of Optically Active Isocyanide.—A mixture of 2 mmol of isocyanide and 104 mg (0.4 mmol) of copper(II) acetylacetonate in 3 ml of chloroform was allowed to stand at 20° for 5 hr. The racemization degrees of α-phenylethyl isocyanide, α-(*p*-chlorophenyl)ethyl isocyanide, and α-(*p*-methoxyphenyl)ethyl isocyanides were 39, 49, and 17%, respectively.

Reaction of Isocyanides with Carbonyl Compounds.—A mixture of isocyanide (10 mmol), carbonyl compound (20 mmol), and Cu_2O (0.20 mmol) in benzene (3 ml) was heated at 80°. The reaction product, a derivative of Δ^2-oxazoline, was isolated by fractional distillation. The reaction time and the product yield

(11) "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 506.

TABLE VI

PRODUCTS FROM ISOCYANIDES AND CARBONYL COMPOUNDS



5

Compd	R^1	R^2	R^3	R^4	Bp, °C (mm)	—Calcd (found)— C, %	H, %	N, %	Principal ir bands, cm^{-1}	Nmr, τ (in $CDCl_3$)	Isomer ratio
5a	Ph	H	Me	Me	79–80°(7)	75.40 (74.81)	7.48 (7.47)	7.99 (7.94)	1618 (w)	9.15 and 8.42 (2 s, CH_3), 5.17 (d, ≥CH), 3.01 (d, N=CH), and 2.75 (s, Ph)	No isomer
5b	Ph	H	Ph	Me	116–117°(3)	80.98 (81.27)	6.37 (6.41)	5.90 (6.02)	1618 (w)	8.81 (s, CH_3), 4.80 (d, ≥CH), 2.74 and 2.64 (2 s, Ph and overlap N=CH)[a] 8.16 (s, CH_3), 4.92 (d, ≥CH), and 2.84 broad s, Ph and N=CH)[a]	2.0/1.3
5c	Ph	H	$-(CH_2)_4-$		106–107°(0.8)	77.58 (77.34)	7.51 (7.62)	6.96 (6.81)	1630 (s)	9.00–7.60 (m, H-1 of cyclopentyl), 5.30 (d, PhCH<), 2.96 (d, N=CH), and 2.74 (m, Ph)[b]	No isomer
5d	Ph	H	*i*-Pr	H	77°(3)	76.15 (76.05)	7.99 (8.21)	7.40 (7.44	1620 (w)	9.00, 8.98 (2 d, Me_2CH), 8.12 (m, Me_2CH), 5.87 (t, Me_2CHCH<), 5.21 (d, PhCH<), 3.00 (d, N=CH), and 2.75 (s, Ph)[b]	*c*
5e	Ph	Me	Me	Et	79–80°(6)	76.81 (77.11)	8.43 (8.67)	6.89 (7.16)	1618 (w)	9.30 (s, CH_3CEt), 8.54 (major), 8.46 (minor) (2 s, $PhCCH_3$), 7.7–9.3 (m, CH_3CH_2), 3.18 (s, N=CH), and 2.70 (m, Ph)[b]	3/5
5f	CO_2Et	H	Ph	Me	107–113°(0.2)	66.93 (66.63)	6.48 (6.54)	6.01 (5.76)	1625 (w), 1735 (s)	9.20 (t, CH_3CH_2), 8.15 (s, CH_3), 6.38 (q, CH_3CH_2), 5.40 (s, ≥CH), 2.68 (s, Ph), and 2.60 (d, N=CH)[a] 8.65 (2 t, CH_3CH_2), 8.36 (s, CH_3), 5.66 (q, CH_3CH_2), 5.35 (s, ≥CH), 2.68 (s, Ph), and 2.60 (d, N=CH)	1.0/1.0
5g	CO_2Et	H	*i*-Pr	H	110°(6)	58.36 (58.46)	8.16 (8.44)	7.56 (7.30)	1615 (w), 1730 (s)	9.00 (d, each peak is d, $(CH_3)_2CH$), 8.66 (t, CH_3CH_2), 8.10 (m, Me_2CH), 5.70 (q, CH_3CH_2), and 3.04 (d, N=CH)[b]	*c*
5h	CO_2Et	H	$-(CH_2)_4-$		81–84°(0.5)	60.89 (60.13)	7.67 (7.81)	7.10 (7.11)	1630 (m), 1750 (s)	8.65 (t, CH_3), 8.66 (broad s, H-1 on cyclopentyl), 5.73 (q, CH_3CH_2), 5.43 (d, ≥CH), and 3.02 (d, N=CH)	No isomer

[a] Each of the two configurational isomers were separated by glpc. Their nmr absorptions are given here separately. Isomer ratio was calculated from the glpc peak areas and confirmed by the corresponding nmr absorption intensity ratio of the isomer mixture. [b] Two isomers were not separated by glpc. Nmr absorption of a mixture of the two isomers are given here. The isomer ratio of **5e** was determined by the Me intensity of the nmr spectrum. [c] Two isomers could not be separated by glpc. There nmr spectra show the presence of two isomers, but the ratio could not be determined due to close peaks of isomers.

are shown in Table III. Identification data of the products are summarized in Table VI.

Registry No.—**3a,** 31385-48-5 (isomer a), 31339-14-7 (isomer b); **3b,** 31339-15-8 (a), 31339-16-9 (b); **3c,** 31385-49-6 (a), 31339-17-0 (b); **3d,** 31339-18-1 (a), 31339-19-2 (b); **3e,** 31339-20-5 (a), 31339-21-6 (b); **3f,** 31339-22-7 (a), 31339-23-8 (b); **5a,** 31339-24-9; **5b,** 31385-50-9 (a), 31339-25-0 (b); **5c,** 31339-26-1; **5d,** 31339-27-2 (a), 31339-28-3 (b); **5e,** 31339-29-4 (a), 31339-30-7 (b); **5f,** 31339-31-8 (a), 31339-32-9 (b); **5g,** 28082-06-6 (a), 28082-01-1 (b); **5h,** 31339-35-2; **6a,** 31339-36-3; **6b,** 31385-51-0; **6c,** 31428-84-9; **6d,** 31339-37-4; **6e,** 31339-38-5; **6f,** 31339-39-6; **6g,** 31339-40-9; **6h,** 31339-41-0; **7a,** 31339-42-1; **7b,** 31339-43-2; **7c,** 31339-44-3; **7d,** 31339-50-1 (a), 31339-51-2 (b); **7e,** 31339-45-4; **7f,** 31339-46-5; **7g,** 31339-47-6; **7h,** 31339-48-7; **8a,** 31385-52-1; **8b,** 31339-49-8 (a), 31339-52-3 (b); **8e,** 31339-53-4; Δ^1-**18,** 31339-54-5; Δ^2-**18,** 31339-55-6; **19,** 31339-56-7; **20,** 31339-57-8; **21,** 31328-34-4; (+)-α-phenylethylamine, 3886-69-9; (+)-α-(*p*-chlorophenyl)ethylamine, 27298-99-3; (+)-α-(*p*-methoxyphenyl)ethylamine, 22038-86-4; (+)-α-phenylethyl isocyanide, 21872-33-3; (+)-α-(*p*-chlorophenyl)ethyl isocyanide, 31328-39-9; (+)-α-(*p*-methoxyphenyl)ethyl isocyanide, 31328-40-2.

Halogenation with Copper(II) Halides. Halogenation of Olefins with Complexed Copper(II) Halides

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A new method for the halogenation of olefinic bonds without the utilization of molecular halogens is described. This synthetic technique is based on the reaction of olefins with copper(II) halides in the presence of strong coordinating agents. Simple olefins are converted to vicinal dihaloalkanes in good to excellent yields. Conjugated diolefins experienced predominately 1,4 addition. Complexed copper(II) halides in combination with different halide donors afforded an *in situ* synthesis of pseudohalogen compounds, which yielded ultimately chloroiodo- and chlorobromoalkanes. The general scope of these reactions has been demonstrated for a variety of olefinic substrates and for a number of ligands. The synthetic utility and the mechanistic implications of these reactions are discussed.

While substitutive halogenation of reactive organic compounds by copper(II) halides has been known for several decades,[1] halogen addition in copper(II) halide–olefin reactions has been observed relatively recently. These addition reactions have involved either vapor phase halogenation over supported copper(II) halides[2] or liquid phase reactions at temperatures exceeding 100°.[3] Under these circumstances thermal dissociation of the copper salt was considered to be an important factor.

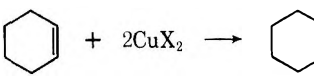
A previous paper from this laboratory has described copper(II) bromide–olefin systems where bromination occurred spontaneously at room temperature and was not dependent on thermal treatment.[4] These results were rationalized on the basis of the influence of copper ion complexation on the reaction. This view was predicated on the known sensitivity of the relative stabilities of metal ion oxidation states to coordination with strong π-bonding ligands.[5,6] In this case ligand induced dissociation of copper(II) halide in the presence of olefin yielded the corresponding halogen addition product (eq 1).[4,7-9]

$$CuX_2L_m \rightleftharpoons CuXL_n + {}^1/_2X_2 \xrightarrow{C=C} XCCX \qquad (1)$$
$$L = \text{ligand}$$

On the basis of these preliminary results a general investigation of the ability of complexed copper(II) halides to function as selective olefinic halogenation reagents was initiated. This paper presents the synthetic chemistry that has evolved from this program.

Results

Ligands for Copper(II) Halide Halogenation.—Potential ligands for copper(II) halide halogenation were screened utilizing the reaction of cyclohexene with copper(II) chloride and bromide as a model system (eq 2). Effective ligands are listed in Table I. Liquid



$$+ 2CuX_2 \longrightarrow + 2CuX \qquad (2)$$

ligands were employed in stoichiometric excess; if a solid ligand, or a catalytic quantity of a ligand, were involved, the reaction was performed in excess olefin or a suitable inert diluent.

The most beneficial ligands were those nitrogen, phosphorus, and sulfur compounds that stabilize copper(I) through strong back donation.[5] Acetonitrile emerged as a particularly useful reagent due to its effectiveness as a stabilizing ligand[6,8b,10] and the simplicity of the synthetic procedure. Powerful complexing agents like hexamethylphosphoramide, tetramethylguanidine, *N,N,N′,N′*-tetramethylethylene- and -propanediamine were totally ineffective, a reflection of the preferential stabilization of copper(II) by these *n* donors.[5] That the olefinic bond itself can promote halogenation[4,11] is evidenced by reaction in solvents whose coordination with metal ions has no π component and a weak to moderate σ bond. Representative of these diluents are oxygenated compounds and dimethylformamide, which are included in Table I for convenience although they are not ligands in the strictest sense. Their function is to solubilize the reactants.

All of the ligands in Table I were capable of achieving bromination; only nitriles were effective for chlorination. This distinction is attributed to two factors. One was the relative lability of the copper(II) salts toward ligand-induced dissociation.[9a] The other was

(1) Acetone: (a) V. Kohlschutter, *Chem. Ber.*, **27**, 1110 (1904). Ketones olefins: (b) J. K. Kochi, *J. Amer. Chem. Soc.*, **77**, 5274 (1955); (c) J. K. Kochi and D. M. Mog, *ibid.*, **87**, 522 (1965), and references cited therein; (d) E. R. Glazier, *J. Org. Chem.*, **27**, 2937, 4397 (1962); (e) P. B. Sollman and R. M. Dodson, *ibid.*, **26**, 4180 (1961); (f) K. B. Doifode and M. G. Marathey, *ibid.*, **29**, 2025 (1964); (g) L. C. King and G. K. Ostrum, *ibid.*, **29**, 3459 (1964); (h) A. W. Fort, *ibid.*, **26**, 765 (1961); (i) E. W. Kosower, W. J. Cole, G. S. Lou, D. E. Cardy, and G. Meisters, *ibid.*, **28**, 630 (1963); (j) E. W. Kosower and G. S. Lou, *ibid.*, **28**, 633 (1963). Aromatics: (k) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963); (l) D. C. Nonhebel, *Proc. Chem. Soc.*, 307 (1961); (m) J. C. Ware and E. F. Borchert, *J. Org. Chem.*, **26**, 2263, 2267 (1961); (n) P. Kovacic and K. E. Davis, *J. Amer. Chem. Soc.*, **86**, 427 (1964). Carboxylic acids: (o) R. Louw, *Chem. Commun.*, 544 (1966). Chelates: (p) R. H. Barker, M. Kato, G. W. McLaughlin, and H. B. Jonassen, *Bull. Chem. Soc. Jap.*, **39**, 1327 (1966).

(2) (a) R. P. Arganbright and W. F. Yates, *J. Org. Chem.*, **27**, 1205 (1962); (b) P. P. Nicholas and R. T. Carroll, *ibid.*, **33**, 2345 (1963); (c) British Patent 907,435 (1962).

(3) (a) H. E. Holmquist, Canadian Patent 771,217 (1967), 771,218 (1967); (b) C. E. Castro, *J. Org. Chem.*, **26**, 4183 (1961); (c) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *ibid.*, **30**, 587 (1965), and references cited therein; (d) T. Kayono, *Bull. Chem. Soc. Jap.*, **43**, 1439, 3501 (1970); (e) K. Ichikawa, S. Uemura, Y. Takagaki, and T. Hiramoto, *Bull. Jap. Petrol. Inst.*, **12**, 77 (1970); (f) M. L. Spector, H. Heinemann, and K. D. Miller, *Ind. Eng. Chem.*, **6**, 327 (1967).

(4) W. C. Baird, Jr., and J. H. Surridge, *J. Org. Chem.*, **35**, 2090 (1970).

(5) H. J. Emeleus and J. S. Anderson, "Modern Aspects of Inorganic Chemistry," Routledge and Kegan Paul Ltd., London, 1960, Chapter 6.

(6) J. C. Barnes and D. C. Hume, *Inorg. Chem.*, **2**, 444 (1963).

(7) W. Schneider and A. V. Zelewsky, *Helv. Chim. Acta*, **46**, 1848 (1963).

(8) (a) J. Gazo, *Chem. Zvesti*, **19**, 826 (1965); *Chem. Abst.*, **64**, 4575c (1966); (b) H. C. Mruthyunjaya and A. R. Vasudeva Murthy, *Indian J. Chem.*, **7**, 403 (1969).

(9) (a) J. N. Cislova, G. Ondrejovic, and J. Gazo, *Z. Chem.*, **6**, 429 (1966); (b) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 1887 (1963).

(10) R. A. Walton, *Quart. Rev., Chem. Soc.*, **19**, 126 (1965).

(11) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience, New York, N. Y., 1966, pp 680, 772.

TABLE I
LIGANDS FOR COPPER(II) HALIDE HALOGENATIONS[a]

Nitrogen compd	Phosphorus compd[b]	Sulfur compd	Oxygen compd
Acetonitrile[b,c]	Triphenylphosphine	Thiophene	Tetrahydrofuran
Benzonitrile[b,c]	Triphenylphosphine oxide	Tetrahydrothiophene	Methanol
Glutaronitrile[b]	Triphenyl phosphite	Sulfolane	Acetic acid
Succinonitrile[b]	Methyl phosphate	Dimethyl sulfoxide	Acetone
Tetracyanoethylene[b]	Methyl phosphite	Sulfur dioxide	
Dimethylformamide	Butyl phosphite		
	tert-Butyl phosphite		
	1,2-Bis(diphenylphosphino-ethane)		
	4-Methyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane		

[a] Yields ranged from 20 to 95%. [b] May be used catalytically for copper(II) bromide bromination. [c] Most effective ligands for copper(II) chloride chlorination.

halogenation of the ligand, particularly those bearing active ring systems (triphenyl phosphite, thiophene) or active hydrogens (alkyl phosphites, dimethyl sulfoxide). This halogenation is believed to occur within the copper(II) complex itself[3c,12] and was particularly prevalent with copper(II) chloride. These difficulties did not manifest themselves in the more labile copper(II) bromide reactions.

The copper(II) halide reactions occurred with a minimum of solvent (ligand) participation to give β-haloalkyl products. The comparative data of Table II

TABLE II
BROMINATION OF CYCLOHEXENE IN VARIOUS MEDIA

Bromine source	Solvent–ligand	Product distribution,[a] % 1,2-Br$_2$-c-C$_6$H$_{10}$	1-Br-2-Y-c-C$_6$H$_{10}$	Ref
$CuBr_2$	CH_3CN	98–100	0–2	
Br_2	CH_3CN	67	33	*b, d*
$CuBr_2$	CH_3OH	79	21	4
Br_2	CH_3OH	35	65	*c*
$CuBr_2$	CH_3COOH	90	10	
Br_2	CH_3COOH	74	26	*c*
$CuBr_2$	$(CH_3)_2CO$	59	41	
Br_2	$(CH_3)_2CO$	25	75	*c*

[a] Cyclohexene conversion, 80–95% in all cases. [b] T. L. Cairns, P. J. Grayham, P. L. Barrick, and R. S. Schreiber, *J. Org. Chem.*, **17**, 751 (1952). [c] F. Boerwinkle and A. Hassner, *Tetrahedron Lett.*, 3921 (1968), and references cited therein. [d] Y = CH_3CONH, CH_3O, CH_3COO, HO radicals.

highlight the differences between these reactions and those of molecular halogen in identical reaction media. Although capture of the reaction intermediate (bromonium ion) by such nucleophilic solvents is anticipated, the predominance of dibromide product in the copper(II) bromide reactions is believed to reflect the participation of a more active bromide ion source than bromide or tribromide ions.

Chlorination with Copper(II) Chloride.—Olefins reacted with copper(II) chloride in acetonitrile or benzonitrile solution to produce vicinal dichloroalkanes in yields of 30–80% (eq 3). The reactions were performed at 60–80° for 2–4 hr, and representative data are presented in Table III. The selectivity to the vicinal dichlorides was essentially quantitative, and

$$RCH{=}CHR + 2CuCl_2 \xrightarrow{RCN} \underset{Cl}{\overset{Cl}{|}}RCHCHR + 2CuCl \quad (3)$$

TABLE III
HALOGENATION OF OLEFINS WITH COPPER(II) HALIDES IN ACETONITRILE

Olefin	Yield of vicinal dihaloalkane, %[a] $CuCl_2$[b] ClCCCl	$CuBr_2$[c] BrCCBr	I_2/$CuCl_2$[d] ICCCl	Br_2/$CuCl_2$[e] BrCCCl
$CH_2{=}CH_2$	32	57	70	
$CH_3CH{=}CH_2$			85[f]	
$CH_3CH{=}CHCH_3$		91[g]		
$(CH_3)_2CCH{=}CH_2$	17	91	73	
$(CH_3)_2C{=}C(CH_3)_2$	53	91		
Cyclohexene	73[f]	80[i]	95[i]	55[i]
$PhCH{=}CH_2$		87	75[m]	
Norbornene	68[g]			
$CH_2{=}CHCH{=}CH_2$	43[h]	92[k]	90[h]	
Cyclopentadiene			70[n]	
$CH_3CH{=}CHCOOCH_3$		49[b]		
$CH_2{=}CHCl$			81[o]	
$CH_2{=}CHCN$		32[b]		
$CH_2{=}CHOOCCH_3$			83[p]	

[a] Based on olefin or copper(II) halide charged. [b] 60–80°, 2–4 hr. [c] 25°, 5–15 min. [d] 25–60°, 30–60 min. [e] 80°, 1 hr. [f] 93–97% trans. [g] Mixture of isomers. [h] 80% trans 1,4; 5% cis-1,4; 15% 3,4. [i] Cis → *dl*; trans → meso. [j] 100% trans. [k] 100% 1,4. [l] 76% 1-chloro-2-iodo, 24% 1-iodo-2-chloro. [m] 1-Chloro-2-iodo-1-phenylethane. [n] 85% 3,5; 15% 3,4 dichlorides. [o] 73% 1-iodo-2,2-dichloro; 27% 1-iodo-1,2-dichloro. [p] 1-Chloro-1-acetoxy-2-iodoethane.

the formation of allylic chlorides was not detected. The anhydrous and hydrated forms of copper(II) chloride were used without any effect on yield or stereochemistry. The addition of an equal molar amount of potassium chloride depressed the yield by a factor of 5 under identical reaction conditions. The deleterious influence of excess chloride ion is ascribed to the competitive formation of polychloro copper(II) complexes.[13] This displacement of the activating nitrile ligand is reflected in a reversal of copper(II) chloride dissociation.

The reactions of the conjugated diolefins, butadiene and cyclopentadiene, merit some discussion. Although both substrates experienced chlorination in acetonitrile, the reactions were markedly sensitive to catalysis by iodine or iodine donors (eq 4; Table IV). The source

$$CH_2{=}CHCH{=}CH_2 + 2CuCl_2 \xrightarrow[\text{catalyst}]{CH_3CN,\ 60°,\ 1.5\ hr} \left.\begin{array}{l} ClCH_2CH{=}CHCH_2Cl\ (85\%) \\ ClCH_2\underset{Cl}{\overset{Cl}{|}}CH{=}CH_2\ (15\%) \end{array}\right\} + 2CuCl \quad (4)$$

(12) J. G. Verkade and T. S. Piper, *Inorg. Chem.*, **1**, 453 (1962).

(13) S. E. Manahan and R. T. Iwamoto, *ibid.*, **4**, 1409 (1965).

TABLE IV

CATALYSIS OF BUTADIENE CHLORINATION IN ACETONITRILE[a]

Catalyst	Mol of $CuCl_2$:mol of catalyst	Yield, %[b]
		43
CuCl	20:1	49
I_2	50:1	80
CuI	40:1	76

[a] 60°, 1.5 hr. [b] Based on copper(II) chloride charged.

of this catalysis was the *in situ* generation, reaction, and regeneration of the interhalogen compound, iodine monochloride. While the synthesis of interhalogen compounds will be developed thoroughly in a subsequent section of this report, some remarks are relevant at this point. The reaction sequence is initiated by the formation of iodine monochloride from copper(II) chloride and iodine (eq 5a). Subsequent addition to

$$CuCl_2 + {}^1/_2I_2 \longrightarrow CuCl + ICl \quad (5a)$$

$$CH_2{=}CHCH{=}CH_2 + ICl \longrightarrow ICH_2CH{=}CHCH_2Cl \quad (5b)$$

$$ICH_2CH{=}CHCH_2Cl + CuCl \longrightarrow ClCH_2CH{=}CHCH_2Cl + CuI \quad (5c)$$

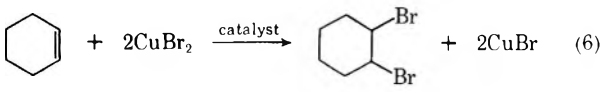
$$ICH_2CH{=}CHCH_2Cl + CuCl_2 \longrightarrow ClCH_2CH{=}CHCH_2Cl + CuCl + {}^1/_2I_2 \quad (5d)$$

$$CuI + CuCl_2 \longrightarrow 2CuCl + {}^1/_2I_2 \quad (5e)$$

butadiene (5b) followed by halogen exchange with either copper(I) chloride (5c) or copper(II) chloride (5d) produced the isomeric dichlorobutenes and released iodine or copper(I) iodide for recycle (5d, 5e). The overall stoichiometry is represented by eq 4, and the catalytic role played by iodine is evident from the sequence 5a–e. The validity of the halogen exchange reactions (5c,5d) has been verified experimentally in control reactions. The observed isomeric distribution between 1,4- and 3,4-dichlorobutenes may reflect either S_N2 and S_N2' exchange reactions between the labile allylic iodide and the copper chlorides or the equilibrium distribution of these dihalides over copper(I) salts in nonaqueous media.[14] The reaction of cyclopentadiene is considered to occur in a similar manner.

Bromination with Copper(II) Bromide.—Olefins reacted readily with copper(II) bromide in the presence of a variety of ligands (Table I) to produce exclusively vicinal dibromoalkanes in high yields (Table III). The reaction conditions were extremely mild, many olefins experiencing bromination at room temperature with reaction periods of 5–15 min. Certain deactivated olefins (Table III) required more forcing conditions. The formation of allylic bromides was not observed under any circumstances.

A unique feature of the copper(II) bromide system was the use of the activating ligands in catalytic quantities. Representative data are presented in Table V using cyclohexene as a model olefin (eq 6). The reac-



(6)

tion was carried out using excess olefin, or an inert alkane or aromatic hydrocarbon, as a diluent. This catalytic activity was not anticipated, for it seemed reasonable that the ligands would be removed from the reaction by coordination with copper(I) bromide. In retrospect, it is suggested that the ligands are released from the copper(I) ion by the formation of the stable copper(I) bromide lattice.[15]

TABLE V

CATALYSIS OF CYCLOHEXENE BROMINATION[a]

Catalyst	Mol of $CuBr_2$:mol of catalyst	Yield, %[b]
		53
Acetonitrile	6:1	87
Triphenylphosphine	5:1	74
1,2-Bis(diphenylphosphinoethane)	18:1	97
tert-Butylphosphite	15:1	98

[a] 25°, 1 hr. [b] Based on copper(II) bromide charged.

A control experiment with neat cyclohexene (eq 6) has shown that under these heterogeneous conditions the pure olefin was less effective in promoting reaction. Solubilization of the copper(II) salt would seem to be a prerequisite for participation by olefin by ligand exchange in the homogeneous phase. Potent olefinic ligands such as butadiene and norbornadiene[16] react sluggishly in pure hydrocarbon media, but facile reaction occurs in methanolic solution[4] or, alternatively, in the presence of a catalytic quantity of ligand.[17,18]

Comparable catalysis has not been observed for copper(II) chloride reactions. This failure is ascribed to a requirement for high ligand concentration in order to encourage dissociation of this less reactive copper salt.

Fluorination with Copper(II) Fluorides.—No successful fluorinations have been realized utilizing a number of copper(II) fluoride–ligand combinations. The major obstacles were the extremely unfavorable fluoride–fluorine oxidation potential and the unstable nature of copper (I) fluoride.[15b]

Synthesis of Interhalogen Compounds. Chloroiodoalkanes.—The ligand-induced dissociation of copper(II) chloride afforded an opportunity for the *in situ* formation and reaction of such interhalogens as iodine and bromine monochloride. This option was predicated on the rationale that the addition of a halogen or halide anion to the copper(II) chloride system would yield a redox reaction that produced the corresponding interhalogens (eq 7). If this redox reaction occurred

$$2CuCl_2 + X_2 \xrightarrow{\text{ligand}} 2CuCl + 2XCl \quad (7a)$$

$$2CuCl_2 + X^- \xrightarrow{\text{ligand}} 2CuCl + XCl + Cl^- \quad (7b)$$

in the presence of an olefin, the subsequent addition reaction would produce vicinal chloro halides. In this way these organic dihalides could be synthesized without the necessity of independently preparing the requisite pseudohalogens from elemental halogens.

Iodine monochloride has been generated and reacted *in situ* by the reaction of molecular iodine or iodide

(14) F. J. Bellringer and H. P. Crocker, British Patent 800,787 (1958).

(15) (a) L. Pauling, "College Chemistry," W. H. Freeman and Co., San Francisco, Calif., 1951, pp 552–555; (b) T. Moeller, "Inorganic Chemistry," Wiley, New York, N. Y., 1952, pp 831–834.

(16) J. M. Harvelchuck, D. A. Aikens, and R. C. Murray, Jr., *Inorg. Chem.*, **8**, 539 (1969).

(17) For example, butadiene is brominated by copper(II) bromide in *n*-heptane containing acetonitrile as a catalyst at room temperature. In the absence of the nitrile the reaction temperature is increased to 75–100° at which point thermal dissociation of the copper salt becomes effective.

(18) The quantities of ligands being used are insufficient to drive the reaction through solubilization of copper(II) bromide *per se*.

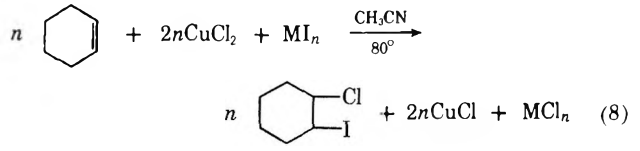
salts with copper(II) chloride. Acetonitrile was utilized as the ligand due to the ease of the procedure and the high reaction rates provided by this medium. Reactions involving molecular iodine occurred at room temperature and were complete within a few minutes. The reaction of gaseous olefins was sufficiently rapid that the reaction was accomplished by simply passing the olefin into the reaction mixture. Some representative examples are found in Table III. Reactions utilizing iodide salts as the iodine source (eq 8) were carried out at 70–80° for 30–60 min. Table VI illustrates the

TABLE VI
IODINE DONORS FOR SYNTHESIS OF CHLOROIODOALKANES[a]

Iodine source (MI_n)	Yield, %[b]	Iodine source (MI_n)	Yield, %
I_2	90	CdI_2	95
HI	94	TiI_4	92
KI	78	SnI_2	82
NH_4I	92	CuI	84
$[Ph_3PCH_3^+]I^-$	95	BaI_2	67
AlI_3	94	$MnI_2 \cdot 4H_2O$	96
FeI_2	86		

[a] 80°, 15–120 min. [b] Based on cyclohexene charged.

types of iodine donors that may be supplied to the reaction; cyclohexene was used as a model olefin, and the stoichiometry was as shown.



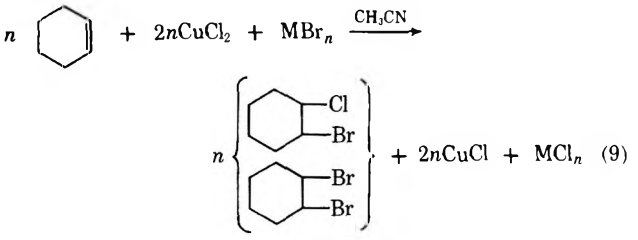
A control reaction in which *trans*-1,2-dichlorocyclohexane was treated with potassium iodide in acetonitrile at 80° for 3 hr yielded the dichloride unreacted. The result demonstrated that the chloroiodide was the true product and did not arise from iodide displacement on initially formed dichloride. In another control experiment 1-chloro-2-iodocyclohexane was refluxed in acetonitrile with copper(II) chloride for 3 hr; no reaction took place indicating that no copper-catalyzed isomerization, elimination, or halide exchange reactions were occurring. Other potential side reactions were effectively suppressed by the solvent, acetonitrile. The reaction with hydrogen iodide (eq 8) was free of any cyclohexyl iodide due to the neutralization of this acid by the basic nitrile. In a similar manner the Lewis acid properties of several of the inorganic by-products, *e.g.*, $AlCl_3$, $SnCl_2$, etc., were neutralized by coordination with acetonitrile. Destruction of the olefin or chloroiodide product through Lewis acid catalyzed alkylation reactions was successfully avoided.

Unsymmetrical olefins yielded chloroiodoalkanes structurally identical with those produced by the addition of preformed iodine monochloride (Table III). Propylene[19] and vinyl chloride[20] gave mixtures of Markovnikov and non-Markovnikov oriented chloroiodoalkanes. Styrene,[21] vinyl acetate,[22] and *tert*-butylethylene[23] gave exclusively the Markovnikov products as anticipated on the basis of electronic and steric effects. The product orientation in all of these cases was consistent with classical iodonium ion SN1 and SN2 mechanisms.[19,21,23]

The reaction of conjugated diolefins has been previously described, and that chemistry is in accord with the *in situ* production and reaction of iodine monochloride. The role played by copper(I) iodide (eq 5c, 5e) is supported by the demonstrated ability of this copper salt to supply iodine to the reaction (eq 8).

Although iodine monochloride has not been isolated from these reactions, the observed chemistry was consistent with the known behavior of this reagent and with the ability of chlorine to oxidize iodide ion. A comparison of these results with those obtained with identical systems in hydrocarbon or chlorocarbon media[22] has shown that different reaction paths and halogen species are involved. While the latter reactions have been found to be sensitive to olefin structure and reaction medium,[22] no such sensitivity has been noted in the present case. The hydrocarbon-based reactions proceeded through molecular iodine addition with Lewis acid catalysis by copper ion; a comparable mechanism in acetonitrile has been precluded by the observed suppression by this solvent of potential Lewis acid catalyzed reactions. Consequently, while no direct evidence for iodine monochloride formation is presented, the participation of this reagent in these systems is deemed reasonable.

Chlorobromoalkanes.—Bromine monochloride was synthesized from combinations of copper(II) chloride and bromine donors in acetonitrile. Cyclohexene, the only olefin studied, was converted to the extent of 50–60% by reaction at 80° for 1 hr (Table III, eq 9).



The product was consistently a mixture of *trans*-1-chloro-2-bromocyclohexane and *trans*-1,2-dibromocyclohexane, a normal by-product of bromine monochloride addition to olefins.[24,25] The use of molecular bromine or copper(II) bromide as a bromine source increased the formation of the dibromide since the higher concentration of bromine facilitated competitive bromination (Table VII). In those cases where bromine was generated by oxidation of bromide ion, traditional bromine monochloride chemistry was observed.

Discussion

It is apparent that coordinated copper(II) halide systems are effective for the facile, selective halogenation of olefins, particularly for the synthesis of vicinal dibromo-, chloroiodo-, and chlorobromoalkanes. Some

(19) C. K. Ingold and H. G. Smith, *J. Chem. Soc.*, 2742 (1931).
(20) M. L. Henry, *C. R. Acad. Sci., Ser. C*, **97**, 1491, (1883); **98**, 370, 518, 680, 741 (1884).
(21) R. E. Buckles and D. F. Knaack, *J. Chem. Educ.*, **37**, 298 (1960), and references cited therein.
(22) W. C. Baird, Jr., J. H. Surridge, and M. Buza, *J. Org. Chem.*, **36**, 2088 (1971).
(23) W. H. Puterbaugh and M. S. Newman, *J. Amer. Chem. Soc.*, **79**, 3469 (1957).
(24) Reference 15b, pp 448, 449.
(25) A. P. Braendlin and E. T. McBee, "Friedel–Crafts and Related Reactions," G. A. Olah, Ed., Wiley, New York, N. Y., 1964, pp 1566, 1567.

TABLE VII
BROMINE DONORS FOR SYNTHESIS OF CHLOROBROMOCYCLOHEXANE[a]

Bromine source (MBr_n)	1-Cl-2-Br-c-C_6H_{10}	Selectivity, %[b]	1,2-Br_2-c-C_6H_{10}
NH_4Br, CuBr, KBr	~93		~7
Br_2, $CuBr_2$	~65–70		~30–35

[a] 80°, 1 hr. [b] Based on cyclohexene charged; cyclohexene conversion ~77%.

remarks concerning the mechanism of these reactions are appropriate at this point. A precise picture of the reaction path has not been developed, but some reasonably consistent statements along these lines can be made. The copper(II) bromide–acetonitrile combination has been utilized exclusively as a model due to the ease of handling this complex system.

Any mechanism proposed for copper(II) bromide bromination must be consistent with the following observations. (1) The reaction occurred with stereospecific trans addition as evidenced by the reactions of cyclohexene and *cis*- and *trans*-butene-2. (2) Norbornadiene reacted with copper(II) bromide in acetonitrile to produce the same mixture of nortricyclic and norbornenyl dibromides as did molecular bromide.[26] (3) *tert*-Butylethylene did not experience any methyl group migration during bromination. (4) A lower level of solvent participation was observed for copper(II) bromide reactions than for bromine (Table I). (5) The relative order of olefin reactivity toward copper(II) bromide parallels that observed for the electrophilic addition of bromine ($R_2C{=}CR_2 > R_2C{=}CHR \gg RCH{=}CHR > RCH{=}CH_2$). (6) The bromination reaction is extremely rapid and commences immediately upon the addition of olefin. (7) Spectrophotometric studies of copper(II) bromide–acetonitrile solutions have shown that the copper(II) salt dissociates according to eq 10a,[7] which is a composite of reactions 10b and 10c. (8) The addition of copper(I) bromide to aceto-

$$2CuBr_2 \rightleftharpoons {}^1/_2Br_2 + Cu^+ + CuBr_3^- \quad (10a)$$

$$CuBr_2 \rightleftharpoons {}^1/_2Br_2 + CuBr \quad (10b)$$

$$CuBr + CuBr_2 \rightleftharpoons Cu^+ + CuBr_3^- \quad (10c)$$

nitrile solutions of copper(II) bromide increases the concentration of $CuBr_3^-$. (9) A spectrophotometric analysis of the reaction of *tert*-butylethylene with copper(II) bromide–acetonitrile shows that the $CuBr_3^-$ concentration increases rapidly to a maximum during the first 10–20% of reaction and then declines gradually. (10) The rate of the reaction does not obey simple first-, second-, or third-order kinetics.[27]

It was initially tempting to interpret this halogenation in terms of ligand induced copper(II) bromide dissociation followed by traditional bromine addition (eq 11). This picture, however, was not consistent with

$$2CuBr_2 \rightleftharpoons 2CuBr + Br_2$$

$$Br_2 + C{=}C \rightleftharpoons \underset{\underset{Br}{|}}{C{-}C^+} \xrightarrow{Br^-} \underset{Br}{\overset{Br}{|}}C{-}C{-}Br \quad (11)$$

(26) S. Winstein and M. Shatavsky, *Chem. Ind. (London)*, 56 (1956).

(27) The second-order kinetics observed in the thermal bromination of unsaturated alcohols with copper(II) bromide[3c] were not noted in this case.

experimental findings. A more reasonable sequence was one initiated by attack on olefin by bromonium ion, or its kinetic equivalent, to generate a normal bromonium ion intermediate. In the early stages of the reaction this removal of "free" bromine would be accompanied by a buildup of copper tribromide ion (eq 10a). Bromide ion transfer from copper tribromide to dibromoalkane and concommitant release of copper(II) bromide yields more bromine *via* reactions 10b and 10c. Repetition of this path leads ultimately to a decline in the $CuBr_3^-$ concentration as the reaction goes to completion.

This reaction scheme is simplistic and has ignored completely the solvating effects of the reaction medium (ion pair interactions, etc.). This study has not attempted to understand these mechanisms in detail, and this aspect of these reactions might justify further probing.

Experimental Section

Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Vapor phase chromatography (vpc) was performed using a Perkin-Elmer 154-D fractometer, a Perkin-Elmer Model 226 capillary gas chromatograph, and a Varian Aerograph Model 202 gas chromatograph. Nmr spectra were recorded on a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Melting points and boiling points are not corrected. Unless otherwise noted, all reagents were obtained from commercial sources and used as received.

Chlorination with Copper(II) Chloride.—In a typical experiment into a round-bottom flask equipped with a reflux condenser were placed acetonitrile (50–100 ml), the olefin (0.05–0.10 mol), and copper(II) chloride (0.10–0.20 mol). The reaction was stirred at 70–80° for 2–20 hr. The inorganic salts were separated by vacuum filtration, and the filter cake was rinsed with pentane. The filtrate was added to 200–500 ml of water, and the product was extracted with pentane (three times, 50–100 ml portions). The combined pentane washings and extracts were washed with water and dried over magnesium sulfate. The pentane was removed on a rotary evaporator, and the yield of dichloroalkane was determined by vpc on a 2 m × 0.25 in. 20% diethylene glycol succinate column at 80° and 15 psig of helium using tetradecane as an internal standard. The dichlorides were purified by distillation and identified by comparison of their physical and spectroscopic properties with those of authentic samples.

Reactions utilizing gaseous olefins were performed in a Parr low pressure reactor[28] at initial olefin pressures of 20–40 psig. The reactor was vented into a trap at −78° to recover any volatile chlorides; no such compounds were recovered. The reaction was worked up as described above.

Bromination with Copper(II) Bromide. Acetonitrile.—The general procedure was identical with that described for copper(II) chloride. The reaction was carried out at room temperature for 5 min to several hours or at 60–80° for 0.5–4 hr. The conclusion of the reaction was indicated by the precipitation of copper(I) bromide. The reaction work-up was performed as above; the pentane and excess olefin were removed on a rotary evaporator at 60° (14 mm). Vpc analysis utilized the same diethylene glycol succinate column at 125–175° and 15–30 psig of helium. The dibromides were identified by comparative techniques. Gaseous olefins were reacted utilizing either a Dry Ice condenser or a Parr low pressure reactor.

Ligands for Copper(II) Bromide Bromination.—Table VIII lists various ligands that were effective for bromination of olefins with copper(II) bromide. Cyclohexene was used as a model olefin, and the general procedure was identical with that described for acetonitrile.

Halogenation of Butadiene. Chlorination.—Into a Parr low pressure reactor were placed 100 ml of acetonitrile and 27 g (0.2 mol) of copper(II) chloride. The reactor was pressurized with butadiene to 20 psig at room temperature, and the reaction mixture was rocked at 60° for 1–2 hr. The reaction mixture was poured into 300 ml of water and was extracted with pentane

(28) Parr Instrument Co., Moline, Ill.

TABLE VIII
LIGANDS FOR COPPER(II) BROMIDE BROMINATION

Ligand	Mol of $CuBr_2$	Temp, °C	Time, hr	Yield, %
Dimethylformamide[a] (50 ml)	0.065	70	1	55
Dimethyl sulfoxide[a] (100 ml)	0.135	70	1	51
Sulfur dioxide[a] (50–75 ml)	0.086	25	10	100
Thiophene[a] (50 ml)	0.045	25	1	87
Tetrahydrothiophene[a] (50 ml)	0.09	25	2	57
Sulfolane[a] (50 ml)	0.09	25	2	66
Tetrahydrofuran[a] (50 ml)	0.09	25	2	100
Acetonitrile[b] (1.1 g, 0.027 mol)	0.18	25	0.3	87
Succinonitrile[b] (1.0 g, 0.013 mol)	0.09	25	1	92
Triphenyl phosphine[b] (5.0 g, 0.02 mol)	0.09	25	1	74
Trimethyl phosphate[b] (5.0 g, 0.035 mol)	0.09	25	1	79
1,2-Bis(diphenylphosphinoethane)[b] (2.0 g, 0.005 mol)	0.09	25	1	97
tert-Butyl phosphite[b] (1.5 g, 0.006 mol)	0.09	25	1	98
$CH_3C(CH_2O)_3P$[b,c] (1.0 g, 0.006 mol)	0.09	25	24	86
$CH_3C(CH_2O)_3PS$[b,d] (1.0 g, 0.005 mol)	0.09	80	1	74

[a] 0.10 mol of cyclohexene; vpc analysis, 6 ft × 0.25 in. 20% FFAP column, 130°, 120 ml/min of helium, r_t 13.8 min. [b] 50 ml of cyclohexene, ligand catalysis. [c] C. W. Heitsch and J. G. Verkade, *Inorg. Chem.*, **1**, 392 (1962). [d] From thiophosphoryl chloride and 2-methyl-2-hydroxymethylpropane-1,3-diol: R. Ratz and O. J. Sweeting, *J. Org. Chem.*, **30**, 438 (1965).

(three times, 50-ml portions). The extracts were washed with water and dried over magnesium sulfate. The pentane was removed on a rotary evaporator, and the crude product was distilled to give a 43% yield of isomeric dichlorobutenes, bp 150–155°. The products were identified by comparative vpc and nmr analysis with authentic samples. Vpc analysis (2 m × 0.25 in. 20% diethylene glycol succinate column, 125°, 15 psig of helium) gave the following isomeric distribution: 3,4-dichlorobutene-1, r_t 2.9 min, 15–19%; *cis*-1,4-dichlorobutene-2, r_t 8.0 min, 3–7%; *trans*-1,4-dichlorobutene-2, r_t 9.6 min, 75–81%.

Bromination.—Butadiene was passed into a stirred solution of 15 g (0.067 mol) of copper(II) bromide in 100 ml of acetonitrile at room temperature for ~10 min. The reaction mixture was filtered; the filtrate was poured into 300 ml of water and was extracted with pentane. The extract was washed with water and dried over magnesium sulfate; the pentane was removed on a rotary evaporator at 60° (14 mm) to give 6.5 g (92%) of *trans*-1,4-dibromobutene-2, mp 52–53° (lit. mp 53–54°).[29] Vpc and nmr analysis showed the dibromide to be a single compound.

Synthesis of Chloroiodoalkanes. Ethylene.—Into a 1-l. flask were placed 500 ml of acetonitrile, 135 g (1.0 mol) of copper(II) chloride, and 130 g (0.51 mol) of iodine. Ethylene was passed into the reaction mixture for 35 min at room temperature; the reaction was stirred vigorously during the introduction of the olefin. The conclusion of the reaction was indicated by the discharge of the iodine color and the precipitation of copper(I) chloride. The reaction mixture was filtered, and the filter cake was washed with 100–200 ml of pentane. The filtrate was poured into 1500–2000 ml of water, and the product was extracted three times with 100-ml portions of pentane. The combined pentane solutions were washed with water, dried over magnesium sulfate, and concentrated on a rotary evaporator at 60° (20 mm). The yield of 1-ehloro-2-iodoethane was 130–140 g (69–74%). The dihalide was shown to be identical with an authentic sample.[22]

Propylene.—A Parr low pressure reactor was charged with 100 ml of acetonitrile, 27 g (0.20 mol) of copper(II) chloride, 27 g (0.11 mol) of iodine, and propylene (20 psig). The reaction was rocked at 50° for 2 hr. The work-up (as above) gave 34.8 g (85%) of chloroiodopropanes.[22] Nmr analysis of the methy group areas showed the product composition to be 76.5% 1-iodo-2-chloropropane and 23.5% 1-chloro-2-iodopropane.

Styrene.—To 100 ml of acetonitrile were added 13.3 g (0.1 mol) of copper(II) chloride, 8.7 g (0.05 mol) of potassium iodide, and 5.2 g (0.05 mol) of styrene. The reaction was stirred at 80° for 1 hr; the product was isolated in the normal manner to give 10.1 g (75%) of 1-chloro-2-iodo-1-phenylethane, mp 36–37° (lit. mp 37–39°).[21,22]

Vinyl Chloride.—The procedure was the same as that described for propylene except the reaction period was 15 hr. The yield of dichloroiodoethane was 36.4 g (81%): bp 31–32° (2.5 mm); $n^{25}D$ 1.5672 (lit. $n^{20}D$ 1.5774);[23] nmr (neat) δ 3.90 (d, 1.4 H, ICH_2), 4.15 (m, 0.6 H, $ClCH_2$), 5.65–6.00 (m, 1 H, X_2CH). Analysis of the spectrum gave a composition of 70% 1-iodo-2,2-dichloroethane and 30% 1,2-dichloro-2-iodoethane.[23]

Anal. Calcd for $C_2H_3Cl_2I$: C, 10.68; H, 1.34; Cl, 31.54; I, 56.44. Found: C, 11.03; H, 1.47; Cl, 31.72; I, 55.57.

In a similar manner vinyl acetate was reacted at room temperature for 2 hr to give an 83% yield of 1-chloro-1-acetoxy-2-iodoethane.[22]

Butadiene.—Into a Parr low pressure reactor were placed 100 ml of acetonitrile, 27 g (0.2 mol) of copper(II) chloride, 1 g (0.004 mol) of iodine or 1 g (0.005 mol) of copper(I) iodide, and butadiene (20 psig). The reaction was agitated at 60° for 90 min. After the standard work-up a 76–80% yield of isomeric dichlorobutenes was recovered. The isomer distribution was identical with that obtained in the absence of iodine catalysis (see above).

An authentic sample of 1-chloro-4-iodobutene-2[30] (1 g, 0.0046 mol) was stirred for 90 min at 50° in 10 ml of acetonitrile with 1 g (0.0075 mol) of copper(II) chloride, or with 1 g (0.010 mol) of copper(I) chloride. The inorganic salt was separated by filtration, and the acetonitrile filtrate was added to 25 ml of water. The product was extracted with pentane, and the extract was analyzed by vpc. In both cases a mixture of isomeric dichlorobutenes comparable to that described previously was present. No chloroiodide remained unreacted.

Cyclopentadiene.—To 500 ml of acetonitrile were added 270 g (2 mol) of copper(II) chloride, 6 g (0.024 mol) of iodine, and 80 g (1.2 mol) of freshly distilled cyclopentadiene. Benzene or cyclohexane (500 ml) was added as an inert diluent, and the reaction was stirred vigorously at room temperature for 15 hr. The reaction mixture was vacuum filtered, and the filtrate was poured into 500–700 ml of water. The hydrocarbon layer was separated, and the aqueous layer was extracted three times with 100-ml portions of pentane. The combined organic layers were washed with 15% sodium thiosulfate solution and then with water. The hydrocarbon solution was dried over magnesium sulfate, and the solvent was removed with a rotary evaporator [60° (80 mm)] to give 115–126 g of crude product. Distillation yielded 90–97 g (65–72%) of dichlorocyclopentenes, bp 64–67° (27 mm), $n^{20}D$ 1.5055. Vpc analysis (5 ft × 0.25 in. 20% diethylene glycol succinate column, 109°, 57 ml/min) of the product mixture gave the following composition: *trans*-3,4-dichlorocyclopentene, 16% (r_t 6.4 min); *trans*-3,5-dichlorocyclopentene, 22–29% (r_t 22.6 min); *cis*-3,5-dichlorocyclopentene, 54–61% (r_t 19.6 min). Capillary vpc (300-ft Dow-Corning silicone 550, 40 psig of helium, 12 min at 42°, program at 10°/min to 125°) revealed the presence of three product peaks in essentially the same relative amounts. The nmr spectrum of the product mixture indicated a 3,5-dichlorocyclopentene content of ~88% and a 3,4-dichloro content of ~12%.

Anal. Calcd for $C_5H_6Cl_2$: C, 43.83; H, 4.42; Cl, 51.75. Found: C, 43.58; H, 4.66; Cl, 51.64.

Iodine Donors.—The general procedure was identical with that described above for styrene. The quantity of iodine donor charged was determined according to the stoichiometry of eq 8. Reaction periods ranged from 15–120 min; the reaction was terminated when the precipitation of copper(I) chloride appeared complete.

(29) "Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland, Ohio, 1969.

(30) H. Johnston, U. S. Patent 2,808,444 (1957).

Synthesis of 1-Chloro-2-bromocyclohexane.—To 100 ml of acetonitrile were added 27 g (0.2 mol) of copper(II) chloride, 10 g (0.1 mol) of ammonium bromide, and 8.2 g (0.1 mol) of cyclohexene. The reaction was stirred at 80° for 1 hr, and the work-up was carried out in the usual manner. Distillation of the crude product gave 10.1 g of *trans*-1-chloro-2-bromocyclohexane, bp 74–77° (6 mm), n^{20}D 1.5247.[31] Vpc analysis (5 ft × 0.25 in. 20% FFAP column, 150°, 70 ml/min of helium) showed the product to consist of 93% 1-chloro-2-bromocyclohexane (r_t 12.0 min) and 7% *trans*-1,2-dibromocyclohexane (r_t 18.8 min).

Solvent Participation in Copper(II) Bromide Bromination. Methanol.—The bromination of cyclohexene with methanolic copper(II) bromide has been described.[4]

Acetic Acid.—A mixture of 23 g (0.1 mol) of copper(II) bromide, 8.2 g (0.1 mol) of cyclohexene, 80 ml of acetic acid, and and 1 ml of acetonitrile was stirred at room temperature for 3 hr. Copper(I) bromide began to precipitate after 15 min. The standard work-up gave 8.8 g of product. Vpc analysis (2 m × 0.25 in. 20% diethylene glycol succinate column, 140°, 220 ml/min of helium) gave the following result: 90% 1,2-dibromocyclohexane (r_t 5.0 min); 10% 1-bromo-2-acetoxycyclohexane (r_t 9.0 min). Saponification of the ester gave the bromohydrin, r_t 6.6 min.[32]

Acetone.—To a solution of 8.2 g (0.1 mol) of cyclohexene in 40 ml of acetone was added 2.2 g (0.01 mol) of copper(II) bromide. The reaction was stirred at room temperature for 2 hr. A 3-ml aliquot was withdrawn and added to 1 ml of pentane and 8 ml of water saturated with sodium chloride. Analysis of the pentane layer by vpc (see above) showed 59% dibromide and 41% bromohydrin.

Acetonitrile.—To a stirred solution of 8.2 g (0.1 mol) of cyclohexene in 60 ml of acetonitrile at 0° was added dropwise over 45 min 16 g (0.1 mol) of bromine.[33] The reaction was stirred at 0° for another 45 min and then was poured into 250 ml of water. A white crystalline precipitate separated immediately; the precipitate was removed by filtration and air-dried to give 6 g (27%) of *N*-(2-bromocyclohexyl) acetamide, mp 121–123°. Recrystallization from 50:50 ethyl acetate–methanol gave white needles, mp 124–125° (lit. mp 109–110°)[33].

Anal. Calcd for $C_8H_{14}BrNO$: C, 43.65; H, 6.41; N, 6.36. Found: C, 43.30; H, 6.45; N, 6.25.

The filtrate was extracted with pentane to recover 15.3 g (63%) of *trans*-1,2-dibromocyclohexane.

If the bromination was carried out in the presence of 0.05 mol of copper(I) or copper(II) bromide, no change in the yields of dibromide and bromoamide occurred. These results demonstrated that the copper salts did not induce the decomposition of the bromoamide.

To a stirred solution of 4.1 g (0.05 mol) of cyclohexene in 60 ml of acetonitrile at 0° was added 22.3 g (0.1 mol, bromine equivalent, 0.05 mol) of copper(II) bromide. The copper salt was added in four equal portions at 12-min intervals; the reaction was stirred for an additional 45 min at 0°. The mixture was poured into 250 ml of water, and the solids were separated by filtration. The filter cake was washed thoroughly with pentane (500 ml), and the filtrate was extracted with the pentane washings. The pentane solution yielded 11.3 g (93%) of *trans*-1,2-dibromocyclohexane. The filter cake and the aqueous filtrate were extracted with methylene chloride (five times, 50-ml portions). From this extract was recovered 0.1 g (0.9%) of crude *N*-(2-bromocyclohexyl)acetamide, mp 115–119°.

Mechanism Studies. Relative Rates of Olefins.—Solutions of olefin pairs in acetonitrile were prepared; *n*-hexane was added as an internal standard for vpc analysis. Aliquots of these solutions were added to solutions of copper(II) bromide in acetonitrile; a stoichiometric deficiency of the copper salt was utilized so that total reaction of neither olefin was possible. The reactions were stirred at room temperature for 5 min. Samples (3 ml) were removed and added to 8 ml of water and 1 ml of an alkane solvent that would not interfere with the vpc analysis (*n*-pentane, *n*-heptane, *n*-octane, cyclohexane). Vpc analysis was carried out on a 2 m × 0.25 in. 20% polypropylene glycol (UCON-550B) column, 65°, 150 ml/min of helium. The relative rates were calculated from the equation

$$\frac{k_{\text{olefin A}}}{k_{\text{olefin B}}} = \frac{\log (\text{olefin A}_0/\text{olefin A})}{\log (\text{olefin B}_0/\text{olefin B})}$$

Some rates relative to octene-1 follow: 2-methylbutene-2 (120); *cis*-pentene-2 (80); 2,3,3-trimethylbutene-1 (40); cyclohexene (20); octene-1 (1); 3,3-dimethylbutene-1 (0.25).

Spectrophotometric Studies.—Spectrophotometric studies on the copper(II) bromide–acetonitrile–*tert*-butylethylene systems were performed on a Beckman DK-2 recording spectrophotometer using matched silica cells of 1.00 ± 0.01 cm path length.

Stock solutions of copper(I) and copper(II) bromide in acetonitrile were prepared. A solution of copper(II) bromide (0.0013 *M*) exhibited a copper tribromide ion absorbance at 620 nm, A = 0.320 (log ϵ 3.3).[7] The addition of copper(I) bromide over the concentration range 0.001–008 *M* increased the absorbance to 1.153 corresponding to a three- to fourfold increase in the copper tribromide concentration.

Solutions of copper(II) bromide (0.002–0.003 *M*) and *tert*-butylethylene (0.004–0.008 *M*) in acetonitrile were prepared. Aliquots of the two solutions were mixed at 25.9°, and the course of the reaction was followed by vpc analysis for dibromide product and by spectrophotometric analysis of the copper tribromide ion concentration. The latter increased rapidly over the first 20% of reaction, stabilized briefly (~20–30% of reaction), and then declined. Plots of the reactants *vs.* time did not establish a simple order for either. Attempts to calculate rate constants for overall second- and third-order kinetics gave steadily decreasing values of k as a function of time over the reaction range, 0–35%.[34]

Registry No.—Copper(II) bromide, 7789-45-9; copper(II) chloride, 7447-39-4; acetonitrile, 75-05-8; benzonitrile, 100-47-0; glutaronitrile, 544-13-8; succinonitrile, 110-61-2; tetracyanoethylene, 670-54-2; dimethylformamide, 68-12-2; dimethyl sulfoxide, 67-68-5; sulfur dioxide, 7446-09-5; thiophene, 110-02-1; tetrahydrothiophene, 110-01-0; sulfolane, 126-33-0; tetrahydrofuran, 109-99-9; triphenylphosphine, 603-35-0; trimethyl phosphate, 512-56-1; 1,2-bis(diphenylphosphino)ethane, 31572-37-9; *tert*-butyl phosphite, 31572-38-0; $CH_3C(CH_2O)_3P$, 1449-91-8; $CH_3C(CH_2O)_3PS$, 3196-56-3; methanol, 67-56-1; acetic acid, 64-19-7; acetone, 67-64-1; cyclohexene, 110-83-8; butadiene, 106-99-0; ethylene, 74-85-1; propylene, 115-07-1; styrene, 100-42-5; vinyl chloride, 75-01-4; 1-iodo-2,2-dichloroethane, 598-37-8; 1,2-dichloro-2-iodoethane, 31572-42-6; cyclopentadiene, 542-92-7; *trans*-3,4-dichlorocyclopentene, 31572-43-7; *trans*-3,5-dichlorocyclopentene, 31572-44-8; *cis*-3,5-dichlorocyclopentane, 31572-45-9.

(31) H. J. Hageman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 1141 (1966).

(32) Table II, ref *c*.

(33) Table II, ref *b*.

(34) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961.

Organometallic Photochemistry. III. The Photolysis of o-Anisyllithium[1]

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The photolysis of *o*-anisyllithium (1) in diethyl ether with high-pressure mercury arc radiation yields, after hydrolysis, 17% 2-methoxybiphenyl (**3**). Smaller quantities (1%) of 2,2′-dimethoxybiphenyl (**4**) are also found. Reaction of the photolysis mixture with deuterium oxide yields 2-methoxybiphenyl-d_1, of uncertain structure, and carbonation gives 2′-methoxy-2-biphenylcarboxylic acid. Photolysis of a mixture of 1 and *n*-butyllithium results in no **3** or **4**; *n*-butylbenzene is the major aromatic product. Various mechanistic pathways are discussed for the rationalization of these results. Under similar conditions, the photolysis of *m*-anisyllithium gives lithium metal and the simple coupling product, 3,3′-dimethoxybiphenyl (8%).

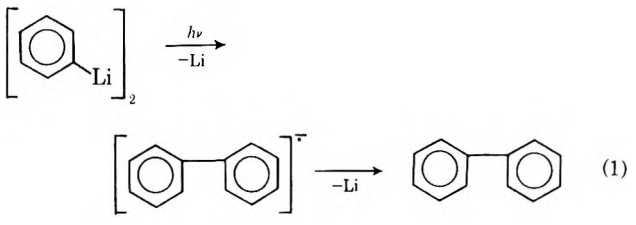
In 1965, van Tamelen and coworkers reported biphenyl yields of 80% from the photolysis of phenyllithium in ether.[2] Although their work suggested a potentially useful synthetic method for the preparation of various biphenyls, no further reports on the photolysis of aryllithiums are known to us. In this paper, we report the results of the photolytic studies of *o*- and *m*-anisyllithium which illustrate two possible photolytic pathways available to substituted aryllithiums.

Results

Preparation of Anisyllithiums.—*o*-Anisyllithium (**1**) was synthesized initially by the metalation of anisole with *n*-butyllithium in ether–hexane. However, the maximum yield of this reaction is only approximately 60%,[3] which we have verified, and the presence of byproducts and unreacted anisole is detrimental to the photolysis process. Therefore, we adopted an alternate route to *o*-anisyllithium in the latter stages of this work, namely, the halogen–lithium exchange reaction. When carried out in hexane solvent, the reaction of *o*-bromoanisole and *n*-butyllithium yields crystalline *o*-anisyllithium which may be separated and redissolved in ether for photolytic studies. This procedure has been used previously for the preparation of phenyllithium[4] and methyllithium,[4] as well as a variety of aryllithiums in the hands of Fraenkel and coworkers.[5] The reaction is of quite high yield (80–90%) and the white, powdery *o*-anisyllithium is uncontaminated except for a trace of lithium bromide. So far, we have applied the technique only for the preparation of *o*- and *m*-anisyllithium, but in view of Fraenkel's work, the method appears to be quite general.

Photolytic Studies.—Photolyses were carried out in all cases with radiation from mercury arc lamps filtered only through quartz. In most cases, a quartz high-pressure mercury arc lamp was used which had usable ultraviolet output from 3660 to 2224 Å. Some photolyses were carried out in a photochemical reactor with low-pressure Hg lamps (2537 Å), but the yields were generally lower. Care was taken to keep the aryllithium solution from contact with air and each photolysis was carried out under an argon blanket. After irradiation of *o*-anisyllithium in ether for an hour or two, the solution began to color pink, and after 12 hr a small amount of precipitate was present. Hydrolysis of the solution and work-up yielded 2-methoxybiphenyl (**3**, 17%), 2,2′-dimethoxybiphenyl (**4**, 1%), as well as 63% recovered anisole. On work-up, the aqueous layer yielded a small quantity (*ca.* 2–3%) of phenolic materials consisting of phenol and various cresols.[6] When allowed to react with deuterium oxide, the photolysis mixture yielded anisole containing 74 and 26% of d_0 and d_1 species, respectively, 2-methoxybiphenyl (16 and 84% d_0 and d_1), and undeuterated 2,2′-dimethoxybiphenyl. Carbonation of the photolysis mixture with Dry Ice–ether slurry gave 2′-methoxy-2-biphenylcarboxylic acid (**5**). This acid was characterized by coversion to the methyl ester **6** with ether–diazomethane, and the nmr and ir spectra of the ester were identical with those of an authentic sample[9] (see Experimental Section).

The results summarized in Scheme I suggest the primary photolytic product to be 2-lithio-2′-methoxybiphenyl (**2**) and are in contrast to the results of van Tamelen, *et al.*,[2] where only biphenyl-d_0 was obtained by deuterolysis of the photolysis mixture from phenyllithium. These workers suggested two possible mechanisms: (a) a route involving the unstable biphenyl radical anion (eq 1) and, (b) synchronous generation and coupling of two phenyl radicals.



(1)

For the present case, the process shown in eq 1 would yield 2,2′-dimethoxybiphenyl radical anion. Although we are uncertain as to the fate of this species under our photolytic conditions, some clue may be derived from the behavior of anisole radical anion, which has been

(1) Paper II in this series: W. H. Glaze, T. L. Brewer, and A. C. Ranade, *J. Organometal. Chem.*, **25**, C6 (1971).

(2) E. E. van Tamelen, J. I. Brauman, and L. E. Ellis, *J. Amer. Chem. Soc.*, **87**, 4965 (1965).

(3) (a) G. Wittig, U. Pockels, and H. Dröge, *Chem. Ber.*, **71**, 1903 (1938); (b) H. Gilman and R. L. Bebb, *J. Amer. Chem. Soc.*, **61**, 109 (1939); (c) D. A. Shirley, J. R. Johnson, Jr., and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 209 (1968); (d) D. W. Slocum, G. Book, and C. A. Jennings, *Tetrahedron Lett.*, 3443 (1970).

(4) T. L. Brown and M. T. Rogers, *J. Amer. Chem. Soc.*, **79**, 1859 (1957).

(5) G. Fraenkel, S. Dayagi, and S. Kobayashi, *J. Phys. Chem.*, **72**, 953 (1968).

(6) The phenolic products may be attributed to the photolysis of anisole,[7] which accumulates at long exposure times.[8]

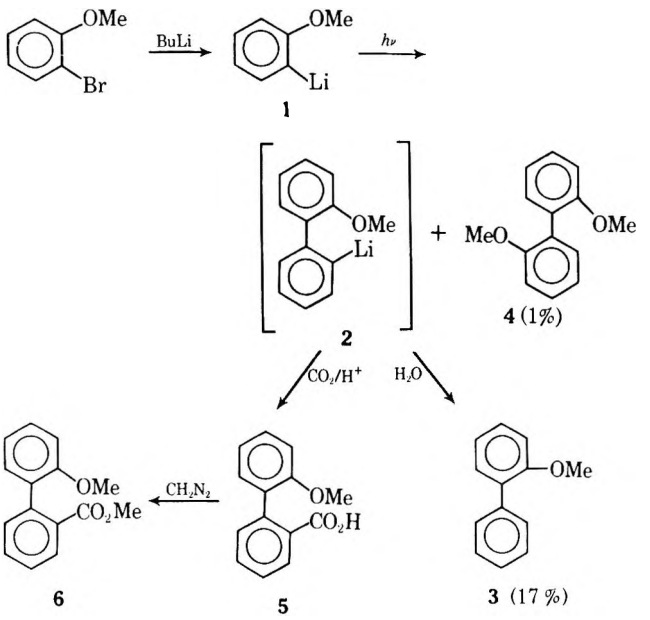
(7) J. J. Houser and M.-C. Chen, *Chem. Commun.*, 1447 (1970).

(8) The large amount of anisole-d_0 and the smaller quantity of 2-methoxybiphenyl-d_0 probably results from the cleavage of ether by the corresponding lithiated species **1** and **2**.

(9) We are grateful to Dr. D. I. Davies for supplying an authentic sample of 2′-methoxy-2-biphenylcarboxylic acid,[10] which upon esterification with diazomethane yielded a methyl ester with identical ir and nmr spectra with the ester obtained from the photolysis of **1**.

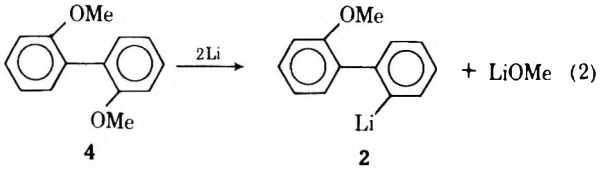
(10) D. I. Davies and C. Waring, *J. Chem. Soc. C*, 1639 (1967).

SCHEME I



studied.[11] Esr spectra indicate that the latter decomposes at room temperature in THF to yield biphenyl radical anion. However, phenol is the major product obtained after hydrolysis.[11] In view of the low yield of phenolic materials which we obtain, it is doubtful that the principal photolytic product **2** would be produced by this route.

Synchronous coupling to yield 2,2′-dimethoxybiphenyl (and lithium metal) may account for the small amount of this material. Moreover, one might propose that the dominant product **2** is produced by cleavage of lithium methoxide from **4** under the photolytic conditions. Some precedent for the cleavage of *o*-methoxy

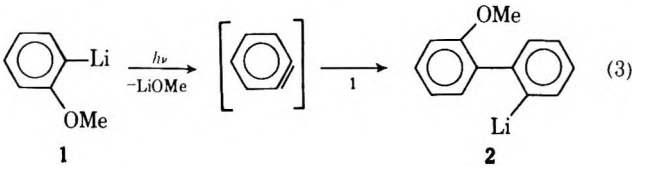


groups in polysubstituted aromatics has been established for Birch reductions,[12] although we are unaware of the occurrence of the reaction with the type of compounds and under the rather mild conditions employed here. To investigate the point further, a sample of **4** was photolyzed in ether with a dispersion of lithium metal. After 24 hr of irradiation under conditions similar to those used for **1**, 90% of **4** was recovered unchanged. Glc of the reaction mixture indicated only a trace of one component which may be attributed to 2-methoxybiphenyl (**3**). In another experiment, the concentrations of **3** and **4** were monitored by removing and hydrolyzing aliquots from the photolysis of **1** at various times. Beginning at 1 hr and observing at 1-hr intervals thereafter, the ratio of **3**:**4** was found by glc to increase from 6 to 21 after 48 hr. In no case was the ratio less than that observed at 1 hr. Thus, reaction 2 must be rather rapid on this time scale if it is to account for the production of **2**.

(11) J. K. Brown, D. R. Burnham, and N. A. J. Rogers, *Tetrahedron Lett.*, 2621 (1966); *J. Chem. Soc. B*, 1149 (1969).

(12) O. L. Chapman and P. Fitton, *J. Amer. Chem. Soc.*, **85**, 41 (1963).

An attractive alternative mechanism would be the photolytic elimination of lithium methoxide to yield benzyne. We expect under these conditions that this intermediate would react with *o*-anisyllithium to yield **2** directly (eq 3).[13,14] Moreover, the probable dimeric



nature of the starting material[15] would provide easy access of the *o*-anisyllithium to the benzyne species before the latter could escape. Unfortunately, the reactive nature of the aryllithiums, as well as the photolytic conditions, makes it difficult to employ the usual benzyne traps. However, photolysis of a mixture of *o*-anisyllithium with *n*-butyllithium (1:2.4) in ether does result in a complete alteration of the photolytic products. Most important, a moderate yield of *n*-butylbenzene (**7**) is observed, as would be expected if the benzyne intermediate were trapped by the excess *n*-butyllithium.[13,14] However, the latter is also undergoing photolysis to some degree under these conditions,[16] and the isolation of **7** cannot be taken as definitive evidence for a benzyne mechanism. Moreover, it appears that the majority of **7** isolated after deuterolysis of the reaction mixture contains two deuterium labels.

While in the process of these trapping experiments, we have discovered a hydrocarbon-soluble complex of *o*-anisyllithium and *n*-butyllithium. This complex, prepared by the reaction of solid **1** with a 1.6 *M* solution of *n*-butyllithium in hexane, has unusual chemical and spectral properties which are presently under investigation.

The photolysis of *m*-anisyllithium has also been investigated and, in accordance with our expectations, yields 3,3′-dimethoxybiphenyl as the only major product (8%) (see Experimental Section). Thus, elimination may be restricted to aryllithiums with polar ortho substituents and may not represent a significant restriction to the use of the photolytic method for the preparation of certain disubstituted biphenyls. Further experiments to explore the method are in progress.[17]

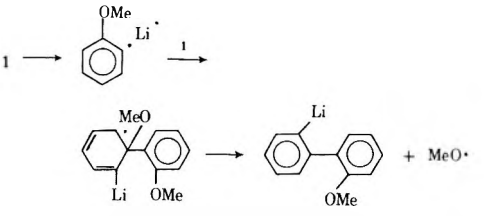
(13) V. Franzen and H. I. Joschek, *Angew. Chem.*, **72**, 564 (1960).

(14) G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956).

(15) P. West and R. Waack, *J. Amer. Chem. Soc.*, **89**, 4395 (1967).

(16) W. H. Glaze and T. L. Brewer, *ibid.*, **91**, 4490 (1969).

(17) A referee has suggested that a radical mechanism should also be considered.



We have no evidence to eliminate this mechanism; in fact, it would be very difficult to distinguish between a "caged radical" and a "caged benzyne" process. However, the marked difference in the behavior of *o*- and *m*-anisyllithium is best explained, we believe, in terms of a benzyne process for the former and a synchronous coupling process for the latter.

Experimental Section

Materials.—Phillips Petroleum Co. pure grade *n*-pentane was redistilled from $LiAlH_4$. Anhydrous diethyl ether obtained from J. T. Baker Co. was dried similarly. *o*- and *m*-bromoanisole were obtained from Eastman Organic Chemicals and were used without further purification. *n*-Butyllithium in hexane (1.6 *M*) was obtained from Foote Mineral Co.

Spectral Measurements.—Spectra were obtained with a Perkin-Elmer Hitachi RMU-7 mass spectrometer, Perkin-Elmer 237 or 621 infrared spectrometers, Cary 14 uv–visible spectrometer, and JEOLCO MH-60 and PS-100 nmr spectrometers.

Preparation of *o*-Anisyllithium.—To a solution of *o*-bromoanisole (23.2 ml, 0.200 mol) in pentane (200 ml) was added a hexane solution of *n*-butyllithium (126 ml, 0.200 mol). The solution was stirred overnight in an argon atmosphere. The reaction vessel was stoppered and taken into a drybox, and the precipitated *o*-anisyllithium was filtered, washed with pentane, and dried. The yield of pure *o*-anisyllithium was 20.0 g (84%). To test the purity, a small portion of o-anisyllithium was dissolved in ether and treated with D_2O. This gave 98% of anisole-d_1, as evidenced by mass spectroscopy. Glc of the organic layer after hydrolysis showed no evidence of benzene or other impurities.

Preparation of *m*-Anisyllithium.—*m*-Bromoanisole (18.7 g, 0.10 mol) was treated with 63 ml of 1.6 *M* *n*-butyllithium (0.10 mol) in hexane as described above. *m*-Anisyllithium was isolated as a white powder and redissolved in dry ether. Glc of an aliquot of the solution showed only anisole after hydrolysis. Deuteriolysis yielded anisole-d_1 (96% isotopic purity).

Photolysis of *o*-Anisyllithium.—A solution of *o*-anisyllithium (11.0 g, 0.096 mol) in ether (450 ml) was irradiated in an immersion photochemical reactor (Ace Glass Co.) with a 450-W Hanovia Model 679A-36 high-pressure Hg arc lamp. The radiation was filtered only through quartz and therefore consisted of a wide distribution of uv wavelengths with maxima at 3660 and 3130 Å. The solution was irradiated for 12 hr under an argon atmosphere, while stirring with a magnetic bar. Deuterium oxide (10 ml) was added slowly through a septum. Glc analysis of a portion of the aqueous layer indicated the presence of methanol. The aqueous layer, on acidification, gave a phenolic material (0.2 g, 2.4%) which was a mixture of phenol and cresols. Removal of volatiles from the dried ether layer gave 8.2 g of a viscous liquid, which upon distillation under vacuum furnished anisole (6.45 g, 0.060 mol), bp 100° (15 mm), and 2-methoxybiphenyl (1.5 g, 0.0082 mol), bp 108° (3 mm). Analysis by mass spectroscopy indicated that the anisole contained 26.1% of anisole-d_1 and 73.9% of anisole-d_0 compounds. The 2-methoxybiphenyl contained 83.5% of d_1 and 16.5% d_0 compounds. The yield of 2-methoxybiphenyl based on initial *o*-anisyllithium is 16.6%, but this amounts to a yield of 45%, based on the *o*-anisyllithium which was photolyzed. Glc analysis of the crude product mixture on a 5 ft × 0.125 in. SE-30 column at 150°, 50-ml/min flow of He, showed the presence of 2,2′-dimethoxybiphenyl (1%). Comparisons of retention times and spectra were made with an authentic sample of 4 collected by preparative glc.[18] In this photolysis, a small amount of polymeric material was also formed.

Carbonation of the mixture after photolysis (0.10 mol of 1 in 300 ml of ether) was accomplished by pouring the mixture over Dry Ice–ether slurry in a glove bag. The alkaline aqueous layer was separated, acidified with hydrochloric acid, and extracted with ether. The mixture of acids (5 and *o*-methoxybenzoic acid) was converted to the corresponding methyl esters with diazomethane–ether and the ester 6 was isolated by preparative glc (5 ft × 0.25 in. SE-30, 220°, 50 ml/min). Mass, nmr, and ir spectra were identical with those of the corresponding ester prepared by treatment of a sample of acid 5 prepared by Davies.[9,10]

Photolysis of *m*-Anisyllithium.—A solution of *m*-anisyllithium (11.0 g, 0.096 mol) in ether (450 ml) was irradiated for 12 hr as described in the previous section. A finely divided dispersion of lithium metal was observed to form during the course of the irradiation. Water (15 ml) was added slowly thereafter. Separation of the organic layer and removal of solvent gave 8.0 g of a dark viscous liquid which upon distillation gave anisole (6.0 g, 0.055 mol), bp 100° (15 mm). Preparative glc of the pot residue yielded 3,3′-dimethoxybiphenyl, the identity of which was established by comparison of ir,[19] nmr,[19] and mass spectra[20] with reported values. The yield of 3,3′-dimethoxybiphenyl (8%) and recovered anisole (52%) was determined by glc. with biphenyl internal standard in a separate run. Thus, the yield of 3,3′-dimethoxybiphenyl based on reacted anisole is 19%.

Control Experiments.—Before photolysis of an ether solution of *o*-anisyllithium, two 20-ml aliquots were removed. Reaction of one with D_2O yielded only anisole-d_1 of 98% isotopic purity. The other aliquot was allowed to stand at room temperature for 12 hr, after which reaction with D_2O gave only anisole-d_1 of 96% isotopic purity. A similar experiment with *m*-anisyllithium resulted in the recovery of anisole-d_1 of 96% isotopic purity immediately after preparation of the solution. However, after standing for 12 hr, the solution gave, upon reaction with D_2O, anisole-d_1 (80%) and anisole-d_0 (20%). The more rapid rate of reaction of *m*-anisyllithium with solvent is apparently responsible for the lower yield of photolysis product, 3,3′-dimethoxybiphenyl.

Photolysis of *o*-Anisyllithium–*n*-Butyllithium Complex.—A mixture of *o*-anisyllthium and *n*-butyllithium (1:2.4 ratio) in ether was photolyzed as in the first experiment. Treatment of the photolysis product with D_2O gave *n*-butylbenzene (2.4% yield), identified by spectral comparison after preparative glc collection. The majority of the *n*-butylbenzene appears to be dideuterated (mass spectroscopy). No 2-methoxybiphenyl was observed by glc from this run; the major products appear to be high polymers of unknown structure.

Preparation of a Soluble Complex of *o*-Anisyllithium and *n*-Butyllithium in Hexane.—A solution of *n*-butyllithium in hexane was added under an argon atmosphere to a suspension of *o*-anisyllithium (4.0 g) in 25 ml of dry pentane. Even after adding 50 ml of *n*-butyllithium some *o*-anisyllithium was still not dissolved. The solution was filtered and evaporated to dryness in a drybox. A crystalline material was obtained which redissolved in dry pentane. Comparison of the integrated areas of aromatic protons of *o*-anisyllithium and of methylene protons α to the lithium atom in *n*-butyllithium indicated that the complex contained 2.4 mol of *n*-butyllithium for each mole of *o*-anisyllithium.

Registry No.—**1**, 31600-86-9; **3**, 86-26-0; *m*-anisyllithium, 31600-88-1; anisole, 100-66-3.

Acknowledgments.—This work was supported by a National Science Foundation grant (GP-9582) and a grant from the North Texas State University Faculty Research Committee. Support from the Robert A. Welch Foundation is also acknowledged. We are grateful to Mr. Don Vieaux for mass spectral work.

(18) D. A. Shirley and W. L. Dean, *J. Amer. Chem. Soc.*, **79**, 1205 (1957).

(19) Sadtler Research Laboratories, Inc., Standard IR Spectrum No. 19573, NMR Spectrum No. 2210M.

(20) C. S. Barnes, D. J. Collins, J. J. Hobbs, P. I. Mortimer, and W. H. F. Sasse, *Aust. J. Chem.*, **20**, 699 (1967).

Photocycloaddition Reactions of 3-Isopropyl-6-methyl-2-cyclohexenone and 3-*tert*-Butyl-2-cyclohexenone

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Received March 1, 1971

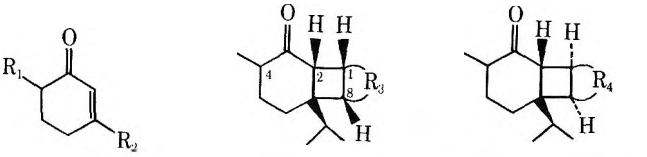
3-Isopropyl-6-methyl-2-cyclohexenone (**1**) has been observed to undergo cycloaddition reactions with cyclohexene, cycloocta-1,5-diene, ethoxyethylene, 1,1-dimethoxyethylene, dimethyl maleate, and dimethyl acetylenedicarboxylate under the influence of ultraviolet light. The structure and stereochemistry of these adducts have been proven by physical and chemical methods. The orientational specificity observed in the photoadducts of **1** to electron-rich olefins, ethoxyethylene, and 1,1-dimethoxyethylene, and the stereochemistry of its dimethyl maleate adduct are explained on the basis of a 1,4-diradical intermediate which closes to a cyclobutane ring. The 3-*tert*-butyl-2-cyclohexenone (**2**) is also found to give 1:1 photoadducts with cyclohexene. Stereochemistry of the cyclobutane–cyclohexanone ring junction in the adducts has been found to be predominantly cis.

The photocycloaddition of α,β-unsaturated ketones to carbon–carbon multiple bonds to give cyclobutane derivatives has been of considerable recent interest,[2] and the cycloaddition reactions have been fruitfully used for the preparation of key intermediates in total syntheses of natural products[3] and cage compounds.[4] In addition, the conjugated ketones have been reported to undergo molecular rearrangements,[5] dimerization,[6] solvent addition,[7] and reduction[8] in the presence of ultraviolet light. Recently, Dauben and coworkers reported the effect of alkylsubstituents on the photochemistry of 2-cyclohexenones[9] and reported that whereas the 3-alkylcyclohexen-1-ones underwent dimerization easily the 3-isopropyl-6-methyl-2-cyclohexenone (carvenone, **1**) and 3-*tert*-butyl-2-cyclohexenone (**2**), were stable to light under normal conditions. They concluded that in these cases the excessive steric hinderance either slows the reaction to the point where demotion from the triplet to the ground state is the only efficient process open to the molecule; or, less likely, decreases the efficiency of S_1–T_1 intersystem crossing. As it is generally agreed, on the basis of experiments involving sensitizers and quenchers, and on the study of emission spectra, that the reactive excited states in dimerization and crossed cycloadditions of 2-cyclohexenones are n–π^* triplets,[10] we thought it of interest to see if 3-alkyl-2-cyclohexenones, sterically hindered for dimerization, could be added photochemically to olefins.[11] A qualitative comparison of the steric requirements for photocycloaddition and photodimerization reactions of cyclic α,β-unsaturated ketones could also prove interesting.

Results

Described below are the photochemical cycloaddition reactions of 3-isopropyl-6-methyl-2-cyclohexenone (carvenone, **1**) to cyclohexene, cycloocta-1,5-diene, ethoxyethylene, 1,1-dimethoxyethylene, dimethyl maleate, and dimethyl acetylenedicarboxylate, and of 3-*tert*-butyl-2-cyclohexenone (**2**), to cyclohexene. Unless stated otherwise, all the photochemical reactions were carried out with a 250-W medium-pressure mercury lamp through a Pyrex filter.

A. Products from Carvenone.—Irradiation of carvenone (**1**) and cyclohexene in benzene for 20 hr afforded the photoadducts **3a** and **4a** in excellent yield (90%), in relative ratio of 2:1, respectively, and were separated by preparative glpc. Both of these compounds, analyzed for $C_{16}H_{26}O$, had their molecular ion corresponding to the 1:1 adduct in the mass spectra, showed the presence of saturated carbonyl and isopropyl groups in their ir, and demonstrated the absence of vinylic protons in the nmr spectra. Based on these analytical and spectral data, the major and the minor



1, R_1 = Me; R_2 = *i*-Pr
2, R_1 = H; R_2 = *tert*-Bu

3a, R_3 = $-(CH_2)_4-$
b, R_3 = $-(CH_2)_2CH=CH(CH_2)_2CH$

4a, R_4 = $-(CH_2)_4-$
b, R_4 = $-(CH_2)_2CH=CH(CH_2)_2CH$

fractions are assigned structures **3a** and **4a**, respectively. Both of these adducts could be chromatographed unchanged on basic alumina and were found to be stable to refluxing sodium methoxide in methanol, showing, therefore, that in both the isomers the cyclobutane–cyclohexanone ring junction is cis and the C-4 methyl group is, probably, equatorial. The nmr spectrum of **3a** showed the C-2 methine proton as a doublet at δ 2.39 (J = 9 Hz), while the same proton in **4a** appeared as a broad singlet at δ 2.6. The large coupling

(1) Synvar Research Institute, Palo Alto, Calif. 94304.

(2) (a) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (b) P. E. Eaton, *Accounts Chem. Res.*, **1**, 50 (1968); (c) T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969); (d) P. G. Bauslaugh, *Syn.*, 287 (1970); (e) P. Boyle, J. A. Edwards, and J. H. Fried, *J. Org. Chem.*, **35**, 2560 (1970); (f) A. I. Meyers and P. Singh, *ibid.*, **35**, 3022 (1970); (g) W. C. Agosta and W. W. Lowrance, Jr., *ibid.*, **35**, 3851 (1970).

(3) P. G. Sammes, *Quart. Rev., Chem. Soc.*, 47 (1970), and references cited therein.

(4) (a) P. E. Eaton and T. W. Cole, *J. Amer. Chem. Soc.*, **86**, 962 (1964); (b) R. C. Cookson, E. Crundwell, R. R. Hill, and J. Hudec, *J. Chem. Soc.*, 3043 (1964); (c) R. C. Cookson, R. R. Hill, and J. Hudec, *ibid.*, 3062 (1964).

(5) O. L. Chapman, *Advan. Photochem.*, **1**, 323 (1963).

(6) (a) O. L. Chapman, P. J. Nelson, R. W. King, D. J. Trecker, and A. A. Griswold, *Recl. Chem. Progr.*, **28**, 167 (1967); (b) P. Yates, S. N. Eğe, G. Büchi, and D. Knutsen, *Can. J. Chem.*, **45**, 2927 (1967).

(7) B. J. Ramey and P. D. Gardner, *J. Amer. Chem. Soc.*, **89**, 3949 (1967).

(8) H. Koller, G. P. Rabold, K. Weiss, and T. K. Makherjee, *Proc. Chem. Soc.*, 332 (1964).

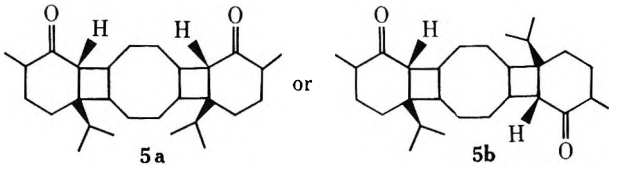
(9) W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *J. Org. Chem.*, **33**, 4060 (1968).

(10) (a) J. L. Ruhlen and P. A. Leermakers, *J. Amer. Chem. Soc.*, **88**, 5671 (1966); (b) P. E. Eaton and W. S. Hurt, *ibid.*, **88**, 5038 (1966); (c) J. L. Ruhlen and P. A. Leermakers, *ibid.*, **89**, 4944 (1967); (d) E. Y. Lam, D. Valentine, and G. S. Hammond, *ibid.*, **89**, 3482 (1967); (e) P. DeMayo, P. J. Pete, and M. F. Tchir, *Can. J. Chem.*, **46**, 2535 (1968); (f) P. DeMayo, A. A. Nicholson, and M. F. Tchir, *ibid.*, **48**, 225 (1970).

(11) A part of this work was published as a preliminary communication: P. Singh, *Tetrahedron Lett.*, 4089 (1970).

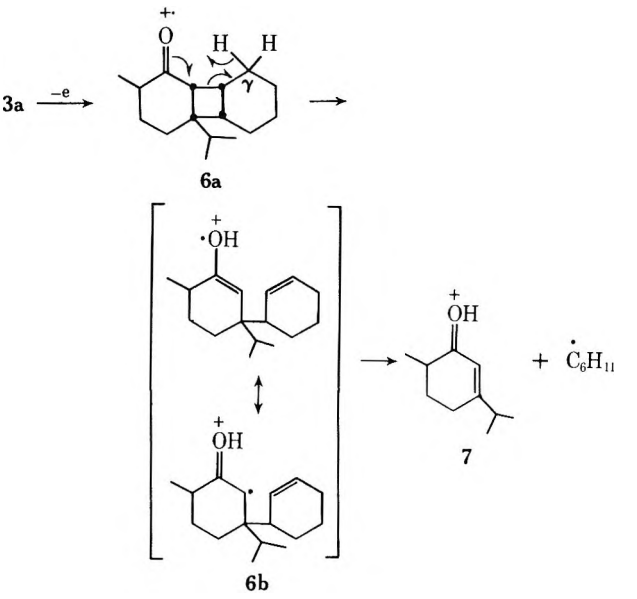
constant obtained for the cyclobutane protons in **3a** requires that they have the syn relationship as shown, and the value is in agreement with those reported in the literature.[12-14] The compound **4a** with a small coupling constant has, therefore, the C-1 and C-2 bridgehead protons anti to each other. Although the stereochemistry at C-8 in both these isomers could not be determined conclusively from the available data, it is very probably cis.

The photocycloaddition of carvenone (**1**) to cycloocta-1,5-diene was relatively slower and gave a 1:1 photoadduct in *ca.* 60% yield after 30 hr of irradiation. This material showed a single spot, in various solvent systems, on a silica tlc plate and gave a sharp-melting 2,4-dinitrophenylhydrazone, mp 165–165.5°. Even though the derivative had a sharp melting point and the adduct showed a single tlc spot, nevertheless, the product was found to be a mixture of two isomers by glpc. The mixture could not be separated by repeated column chromatography on alumina, silica, and Florisil, and by preparative glpc. The mixture was found stable to sodium methoxide in methanol and the two isomers, therefore, represent the photoadducts **3b** and **4b**. In principle, the photoaddition of carvenone to cycloocta-1,5-diene could give a 2:1 photoadduct. Indeed, a minor product, **5**, was obtained by careful chromatography of the crude reaction mixture on basic alumina. From analytical data and molecular weight determination this compound is formulated as $C_{28}H_{44}O_2$. It showed saturated carbonyl and isopropyl absorption bands in the ir spectrum and demonstrated the absence of vinylic protons in its nmr spectrum. The compound **5** could be obtained by further irradiation of the mixture of **3b** and **4b** with carvenone. The minor adduct is thus assigned structure **5** with either the head-to-head (**a**) or the head-to-tail (**b**) orientation of carvenone moieties. The cis fusion of the six- and the four-membered rings is in agreement with the stability of this adduct to basic alumina.

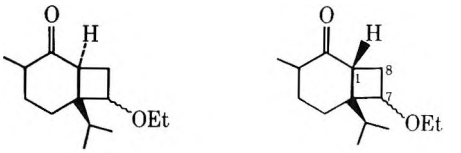


5a **5b**

The 70-eV mass spectrum of the tricyclic ketone **3a** showed a weak molecular ion peak at *m/e* 234 (1%) and low intensity peaks corresponding to the ions resulting from cleavage of the cyclobutane ring at *m/e* 152 (10%) and 82 (8%). In contrast, a strong peak at *m/e* 153, as the base peak, was observed. In general the cyclobutane derivatives are known to give a strong fragment resulting from cleavage of the cyclobutane ring.[15] We attribute the observed fragmentation pattern to the molecule preferentially undergoing McLafferty rearrangement, by transfer of one of the γ hydrogens, to give **6b** over cleavage of the cyclobutane ring. The molecular ion **6b** could readily cleave to give **7**, *m/e* 153. This argument is supported by the observation that the ketone **4a** as well as the mixture of the tricyclic ketones **3b** and **4b** also showed its base peak at *m/e* 153,[16,17] while the bicyclic ketones **9**, **14**, and **15** (see below), devoid of suitably positioned γ protons, exhibited normal cyclobutane cleavage to give an abundant fragment at *m/e* 152.



The photoaddition of 3-isopropyl-8-methyl-2-cyclohexenone (**1**) to ethoxyethylene afforded 1:1 photoadducts in nearly quantitative yield after 6 hr of exposure to a 450-W Hanovia lamp. Analysis of the crude reaction mixture by glpc showed the presence of three compounds in relative ratio of 2:7:1. The

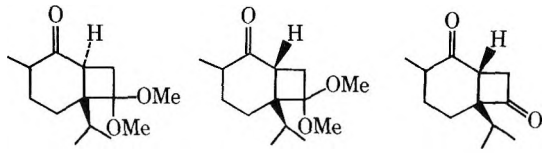


8 **9**

two isomers, obtained in the relative ratio of 2:7, are regarded as having trans and cis stereochemistry, respectively, at the ring junction as the former, **8**, could be isomerized to the latter, **9**, by exposure to basic alumina.[2a] The nmr spectrum of the major product showed its bridgehead C-1 methine proton as a pair of doublets (J_1 = 9 and J_2 = 1.5 Hz), which is in accord with the ethoxy group at C-7 rather than at C-8 position. The position of the ethoxy group was secured by chemical means; for example, treatment of the isomerized photoproduct with sodium methoxide in methanol neither led to replacement of the ethoxy by methoxy group (nmr and glpc analysis) nor accomplished elimination of the ethoxy group to form an unsaturated ketone.[2a] The minor adduct **10** had its spectral data similar to that of the compound **9** and is believed to be the isomer of **9** differing in stereochemistry of the ethoxy group at C-7.

The photochemical reaction of carvenone with 1,1-dimethoxyethylene was also investigated. Under the

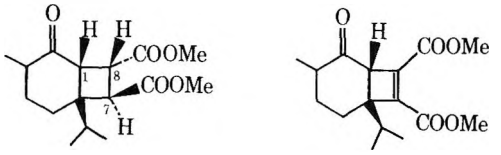
(12) I. Fleming and D. H. Williams, *Tetrahedron*, 2747 (1967).
(13) J. W. Hanifin and E. Cohen, *J. Amer. Chem. Soc.*, **91**, 4494 (1969).
(14) L. Paolillo, H. Ziffer, and O. Buchardt, *J. Org. Chem.*, **35**, 38 (1970).
(15) (a) G. Sugowdz, P. J. Collin, and W. H. F. Sasse, *Tetrahedron Lett.*, 3843 (1969); (b) M. L. Gross and C. L. Wilkins, *ibid.*, 3875 (1969); (c) N. Sugiyama, Y. Sato, and C. Kashima, *Bull. Chem. Soc. Jap.*, **43**, 3205 (1970).
(16) The γ hydrogens in the cis–anti–cis ketone **4a** are not so close to the carbonyl group as in its cis–syn–cis isomer **3a**. However, a slight distortion of the molecule **4a**, conceivably undergoing rapidly at such a high energy as 70 eV, could suitably place these protons for an efficient intramolecular hydrogen transfer. The 15-eV mass spectrum of **4a** indeed showed a strong peak resulting from cleavage of the cyclobutane ring at *m/e* 152 (45%).
(17) P. Singh, *Tetrahedron Lett.*, 1071 (1971).



11 12 13

standard conditions the reaction proceeded readily and afforded two products **11** and **12** in 20 and 80% yield, respectively (overall yield 80%). The former could be isomerized to the latter by basic alumina and must be the trans isomer of **12**. That the methoxyls are at C-7 rather than C-8 was shown by stability of the adduct **12** to sodium ethoxide in ethanol and its acid hydrolysis to the γ diketone **13** (ir spectrum and negative ferric chloride test).

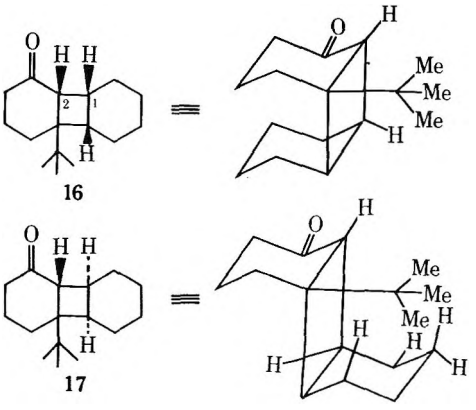
Photocycloaddition of **1** to dimethyl maleate, the electron-poor olefin, was rather sluggish and gave a complex mixture from which the bicycloadduct **14** could be isolated in poor yield (12%). The adduct was stable to basic alumina, supporting cis fusion of the rings. The nmr spectrum (60 MHz), in carbon tetrachloride, showed the bridgehead methine proton as a broad doublet (J = 10 Hz). The large coupling constant is in agreement with the cis relationship of C-1 and C-8 cyclobutyl protons; the broadening of the signal is, presumably, due to long-range coupling with the C-7 proton.[12] The 100-MHz spectrum of the diester **14**, in deuteriochloroform, was very revealing and showed the bridgehead C-1 methine proton as a sharp doublet at δ 2.8 (J = 10 Hz), while the C-7 proton appeared as a doublet at δ 3.52 (J = 3.5 Hz) showing trans relationship of the C-7 and C-8 protons. The trans relationship of the ester groups was further secured by the stability of **14** to sodium methoxide in methanol and to boiling pyridine.



14 15

Carvenone (**1**) was also found to add to acetylenes; thus, irradiation with dimethyl acetylenedicarboxylate afforded 1:1 adduct **15** and the structure is in agreement with its spectral data (see Experimental Section). No other product arising from photorearrangement of the unsaturated diester **15** could be detected.[13] The cycloadduct **15** was stable to basic alumina and pyridine; on this basis the cis fusion shown is assigned.

B. Products from 3-*tert*-Butyl-2-cyclohexenone. — In order to study the effect of a sterically bulkier and electron-donating group at the β carbon of 2-cyclohexenones on photocycloaddition reactions, 3-*tert*-butyl-2-cyclohexenone (**2**) was irradiated with excess cyclohexene. Usual work-up after 30 hr gave a mixture of photoadducts **16** and **17** in moderate yield (37%), in relative ratio of 5:1, respectively. The mixture was stable to basic alumina and boiling pyridine, demonstrating the cis fusion of cyclobutane–cyclohexanone rings in both these isomers. The isomers **16** and **17** were separated by preparative glpc. These compounds, analyzed for $C_{16}H_{26}O$, showed the presence of a saturated carbonyl group in their ir, and demonstrated the absence of vinylic protons in the nmr spectra. Based on the analytical and spectral data, the major and the minor isomers are assigned structures **16** and **17**. Examination of molecular models indicated a severe nonbonded interaction of the *tert*-butyl group with the cyclohexyl protons in the cis-anti-cis adduct **17**, while the same interaction in the cis-syn-cis adduct **16** was relatively less pronounced. Based on this, the major and the minor isomers are assigned structures **16** and **17**, respectively. This is further substantiated by the 100-MHz nmr spectrum of these stereoisomers.



16

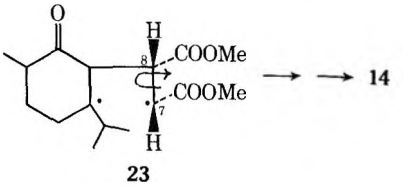
17

Thus, the major isomer **16** showed its C-2 bridgehead methine proton as a doublet with a large coupling constant (J = 9 Hz) as compared to the doublet (J = 2.5 Hz) of the same proton in its stereoisomer **17**.

Discussion of Results

Although a complete product analysis was not undertaken, the present results are consistant with those of the previous workers who have studied the photochemical addition of alkenes to α,β-unsaturated ketones. Thus, the orientational specificity observed in formation of the adducts **8**–**12** is in agreement with Corey's proposal that the complex **18** collapses to give the more stable 1,4 diradical **19**, which recombines to give the products observed.[2a] The diradical **19** should be fairly shortlived, collapsing to cyclobutane products as soon as it is formed, as a relatively long-lived radical **19** could give the unsaturated compound **22** by either of two routes: (a) by intramolecular hydrogen transfer followed by recombination of the diradical thus formed, and (b) by loss of the hydrogen atom to give the radical **21** which could give **22**. Neither the unsaturated compound nor a dimer of **21** could be detected. In fact, carvenone added to ethoxyethylene to give the cyclobutane adducts **8**–**10** in nearly quantitative yield. See Scheme I.

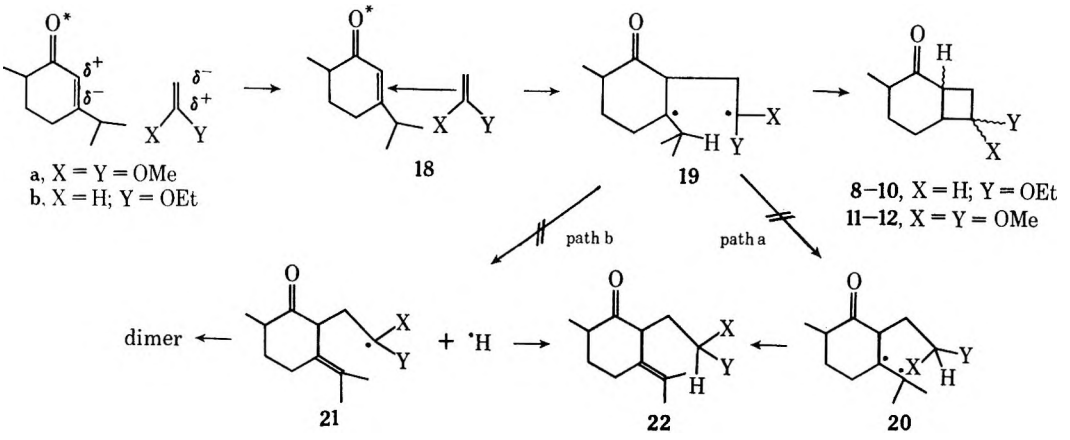
The trans configuration of the methyl ester groups in **14** is also compatible with the diradical mechanism. Rotation about the C-7,C-8 bond in the corresponding diradical **23**, before recombination, would result in the



23

(18) (a) J. Ipaktschi, *Tetrahedron Lett.*, 3179 (1970); (b) W. Kothe, *ibid.*, 5201 (1969); (c) G. Buchi and E. M. Burgess, *J. Amer. Chem. Soc.*, **82**, 4333 (1960).

SCHEME I



formation of thermodynamically more stable product **14**. The poor yield obtained in the photoaddition of dimethyl maleate (and dimethyl acetylenedicarboxylate) to carvenone (**1**), substantiates Corey's observation that substitution of olefins with electron-withdrawing groups is deterious to photocycloaddition reactions.

It might be of interest to note the predominance of cis fusion at the cyclobutane–cyclohexanone ring junction in the photoadducts. Only in the case of electron-rich olefins, ethoxyethylene and 1,1-dimethoxyethylene, did the carvenone give a small amount of the trans-fused adducts. The trans-fused ring junction is normally formed when a 2-cyclohexenone is irradiated with olefins.[2a-d] The reason for this deviation from the normal behavior is still obscure, but our observation has ample precedence in the literature; for example, 3-phenyl-2-cyclohexenone and chromones gave only the cis-fused cyclobutane products when irradiated with various olefins.[2c,13]

In conclusion, it is quite clear that 2-cyclohexenones having sterically bulkier substituents react quite efficiently with olefins under the influence of ultraviolet light. This knowledge extends considerably the synthetic utility of such photocyclizations. These results also indicate that compared to photodimerization the photocycloaddition of 2-cyclohexenone is less sensitive to steric effects.

Experimental Section

Melting points and boiling points are uncorrected. Ir spectra were recorded on a Unicam SP 200 spectrometer. Unless stated otherwise, nmr spectra were recorded on a Varian A-60 spectrometer; the values are given in δ parts per million downfield from tetramethylsilane as internal standard. Mass spectra were recorded on an MS-12 instrument and glpc was run on a Perkin-Elmer F-11 chromatograph using silicone gum rubber (SE-304) as an analytical column. Preparative gas chromatographic separations were accomplished using a 5 ft × ⅜ in. 15% silicone rubber SE-30 on Chromosorb. The general procedure used for irradiation is outlined below.

The apparatus consisted of a cylindrical Pyrex irradiation vessel fitted with a quartz immersion well, a reflux condenser, and a nitrogen inlet. The reactants, with or without a solvent, were thoroughly flushed with nitrogen. The solutions were irradiated, through a Pyrex filter, with a 250-W Hanovia lamp, and a slow stream of nitrogen was kept bubbling through the reaction mixture during the course of irradiation. The progress of the reaction was monitored by drawing aliquots and examining by tlc on silica plates.

3-Isopropyl-6-methyl-2-cyclohexenone (Carvenone, 1).—This terpenoid ketone was obtained as a mobile liquid by a modified procedure of Whiting and coworkers.[19]

A mixture of camphor (304 g, 2 mol) and concentrated sulfuric acid (1.6 kg) was stirred at 110° for 1 hr. The reaction mixture was cooled, diluted carefully with cold water (2 l.), and steam distilled. The steam distillate was extracted with ether. The extracts were washed with a saturated aqueous solution of sodium bicarbonate and with water. The organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil (136 g). Phenol (96 g) was added and fractionation through a 2-ft long vacuum jacketed column gave a mixture of camphor with excess phenol, bp 80–90° (10 mm), followed by carvenone, bp 98–102° (10 mm). The carvenone fraction, containing traces of phenol, was dissolved in ether and washed with 5% aqueous, cold sodium hydroxide and with water. The ethereal layer was dried ($MgSO_4$) and concentrated and distillation on a spinning-band column gave pure carvenone (**1**, 85 g): bp 80–82° (3 mm) [lit.[9] bp 80–81° (3.5 mm)]; ir (neat) 1670, 1630, 1210, and 885 cm^{-1}; nmr (CCl_4) δ 1.26 (d, J = 6 Hz, ring methyl), 1.27 (d, J = 7 Hz, isopropyl methyls) (total 9 H), 1.8–2.5 (m, 6 H, methylene and methine protons), and 5.86 (br, s, 1 H, vinyl proton).

3-*tert*-Butyl-2-cyclohexenone (2).—From 1-*tert*-butylcyclohexene (14.1 g, 0.102 mol), using the procedure of Rao and Dev,[20] there was obtained the title compound **2** (2.7 g, 18%) as a mobile liquid: bp 70–72° (3 mm) [lit.[9] bp 80–81° (4 mm)]; nmr (CCl_4) δ 1.25 (s, 9 H), 1.8–2.5 (m, 6 H), 5.74 (br, s, 1 H).

Photoaddition of Carvenone (1) to Cyclohexene. Formation of 3a and 4a.—A solution of carvenone (4.0 g, 0.026 mol) and cyclohexene (20.5 g, 0.25 mol) in benzene (60 ml) was irradiated for 20 hr. Removal of the solvent and the excess olefin under reduced pressure afforded a mobile liquid, which showed two glpc peaks. The liquid was chromatographed on neutral alumina and elution with *n*-hexane gave **3a** + **4a** as a colorless liquid (5 g, 91%). Although tlc showed only one spot in various solvent systems, glpc showed the presence of two compounds, with the same retention times as for the crude reaction mixture, in relative ratio of 2:1. These compounds were separated by preparative glpc.

The major fraction **3a**, with shorter retention time, was a colorless crystalline solid: mp 52–54° (short-path distillation at 0.5 mm in an oil bath at 80°); ir (CCl_4) 1698, 1383, and 1372 cm^{-1}; nmr ($CDCl_3$) δ 0.77 (d, J = 7 Hz), 0.83 (d, J = 7 Hz), 1.02 (d, J = 6.5 Hz) (total 9 H), 1.13–2.13 (m, 15 H), 2.3–2.8 (m, COCHMe), and 2.39 (d, J = 9 Hz, bridgehead C-2 methine proton) (total 2H); mass spectrum (70 eV) m/e (rel intensity) 234 (1, M^+), 191 (3), 153 (100), 152 (10), 110 (25), 67 (22), 43 (15), and 41 (31).

Anal. Calcd for $C_{16}H_{26}O$: C, 82.05; H, 11.11. Found: C, 81.82; H, 10.91.

The 2,4-dinitrophenylhydrazone was obtained as a deep yellow solid: mp 156–157° (crystallized from methanol); uv max (95% EtOH) 365 nm (ε 25,000), 269 (13,500), and 234 (8000).

(19) C. A. R. Baxter, G. C. Forward, and D. A. Whitting, *J. Chem. Soc. C*, 1162 (1968).

(20) G. S. K. Rao and S. Dev, *J. Indian Chem. Soc.*, **33**, 539 (1956).

Anal. Calcd for $C_{22}H_{30}N_4O_4$: C, 63.75; H, 7.30; N, 13.52. Found: C, 63.68; H, 7.52; N, 13.59.

The minor fraction **4a**, with longer retention time, was obtained as a thick liquid: ir ($CHCl_3$) 1690, 1385, and 1379 cm^{-1}; nmr ($CDCl_3$) δ 0.73 (d, J = 6.5 Hz), 0.77 (d, J = 7 Hz), 1.02 (d, J = 6.5 Hz) (total 9 H), 1.1–2.4 (m, 15 H), 2.6 (br, s, bridgehead C-2 methine proton), and 2.5–2.8 (m) (total 2 H); mass spectrum (70 eV) m/e (rel intensity) 234 (1.5, M^+), 191 (2.5), 153 (100), 152 (7.5), 110 (35), 67 (20), 43 (27), and 41 (20).

Anal. Calcd for $C_{16}H_{26}O$: C, 82.05; H, 11.11. Found: C, 81.76; H, 11.31.

The 2,4-dinitrophenylhydrazone, obtained as deep yellow crystals, had mp 171–172°; uv max (95% EtOH) 366 nm (ϵ 20,000), 265 (9500), and 234 (14,500).

To determine the stereochemistry of the cyclohexanone–cyclobutane ring junction rigorously, the mixture of **3a** and **4a** (107 mg) was refluxed with sodium methoxide (30 mg) in methanol (10 ml), under nitrogen, for 24 hr. The solution was cooled, neutralized with dilute hydrochloric acid, and diluted with water (40 ml). The organic layer was extracted with chloroform and removal of the solvent from the dried ($MgSO_4$) extract gave a colorless liquid. Analysis by glpc showed only **3a** and **4a** and their relative ratio was unchanged.

Photoaddition of 1 to Cycloocta-1,5-diene. Formation of 3b, 4b, and 5.—A solution of carvenone (4.0 g, 0.026 mol) and cycloocta-1,5-diene (9.0 g, 0.082 mol) in benzene (80 ml) was irradiated for 30 hr. Removal of the solvent and the excess diene gave a thick oil, which was chromatographed on an alumina (neutral) column. Earlier eluents with *n*-hexane–diethyl ether (95:5) gave a mixture of **3b** and **4b** as a colorless, mobile liquid (4.2 g, 60%) and later eluents with *n*-hexane–diethyl ether (50:50) gave the adduct **5** as a thick oil (300 mg). The mixture of **3b** and **4b** had ir (neat) 1695 (C=O), 1656 (C=C), 1471, 1397, 1381, and 735 cm^{-1}; nmr ($CDCl_3$) δ 0.7–1.2 (m, 9 H, Me groups of both the isomers), 1.3–2.4 (m, 17 H), and 5.6 (br, t, 2 H, J = 5 Hz, vinylic protons); mass spectrum (70 eV) m/e (rel intensity) 260 (10, M^+), 217 (7), 183 (10), 182 (29), 154 (26), 153 (100), 152 (27), 110 (27), 96 (33), 95 (33), 79 (30), 67 (40), 55 (27), 44 (68), 43 (35), 41 (66), and 39 (37).

The 2,4-dinitrophenylhydrazone, obtained as yellow crystals from hexane–benzene, had mp 165–165.5°.

Anal. Calcd for $C_{24}H_{32}N_4O_4$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.49; H, 7.52; N, 12.67.

Even though the 2,4-dinitrophenylhydrazone had a sharp melting point and the oil obtained above showed a single tlc spot, nevertheless, the product was found to be a mixture of two compounds, **3b** and **4b**, by glpc. The mixture could not be separated into its components by repeated column chromatography on alumina, silica, or forisil, and by preparative glpc. The mixture underwent no change on refluxing for 24 hr with sodium in methanol.

The crude adduct **5** obtained above, rechromatographed on an alumina column, could be crystallized with difficulty from *n*-hexane. Two more crystallizations from the same solvent afforded pure **5**: mp 61–63°; ir ($CHCl_3$) 1690, 1380, and 1370 cm^{-1}. The nmr spectrum showed the absence of a vinylic proton in the compound.

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.72; mol wt, 412. Found: C, 81.78; H, 10.46; mol wt, 408.[21]

The deep orange crystalline bis-2,4-dinitrophenylhydrazone had mp 234–236° and showed the absence of a carbonyl band in its ir spectrum.

Anal. Calcd for $C_{40}H_{52}N_8O_8$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.43; H, 6.93; N, 14.72.

The compound **5** could also be obtained in *ca.* 25% yield when the mixture of tricyclic ketones **3b** and **4b** was further irradiated with carvenone (**1**) for 15 hr.

Photoaddition of Carvenone (1) to Ethoxyethylene. Formation of the Adducts 8, 9, and 10.—Carvenone (**1**, 525 mg) and ethoxyethylene (2 g) in benzene (5 ml) were irradiated in a Pyrex tube with a 450-W Hanovia lamp. After 6 hr the irradiation was stopped; removal of the solvent and the excess olefin gave the 1:1 photoadduct as a light yellow mobile liquid (775 mg, 97%). Analysis by glpc showed three compounds, **8–10** (retention times 12, 14, and 18 min at 108°), in relative ratio of 2:7:1, respectively. The light yellow liquid was chromatographed on basic alumina and analysis by glpc showed the adducts **9** and **10** in a relative ratio of 9:1. The photolysis mixture was separated by preparative glpc. The major component **9** was obtained as a colorless mobile liquid: ir (neat) 1700, 1385, 1375, and 1130 cm^{-1}; nmr (CCl_4) showed the bridgehead C-1 methine proton as a pair of doublets at δ 2.87 (J_1 = 9 and J_2 = 1.5 Hz, 1 H); mass spectrum (70 eV) m/e (rel intensity) 224 (2, M^+), 181 (20), 153 (2.7), 152 (23), 136 (85), 110 (55), 81 (60), 72 (91), 69 (25), 43 (100), and 41 (6).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.75; H, 10.95.

The adduct **8** was also obtained as a liquid. This compound showed the following spectral data: ir (neat) 1703, 1385, 1370, and 1145 cm^{-1}; nmr (CCl_4) showed the C-1 proton at δ 2.95 (doublet of a doublet, J_1 = 8.5 and J_2 = 1.0 Hz, 1 H).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.13; H, 10.85.

The compound **8** was quantitatively isomerized to **9** when passed through an alumina column.

The minor fraction **10**, obtained as an oil, showed bands in its ir spectrum (CCl_4) at 1700, 1380, 1367, and 1170 cm^{-1} and exhibited its C-1 proton as a pair of doublets at δ 2.89 (J_1 = 8.5 and J_2 = 1.5 Hz).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.32; H, 10.53.

In order to determine position of the ethoxy group in the adducts, 100 mg of the isomerized photoproducts **9** + **10** was stirred, at room temperature and under nitrogen, with sodium (70 mg) in methanol (5 ml) for 4 hr. Solid carbon dioxide (excess) was added to decompose sodium methoxide, and the product was extracted with a hexane–ether (1:1) mixture. The extract was dried and removal of the solvents gave an oil (80 mg). This was examined by ir, nmr and glpc and was found to be the completely unchanged starting material.

Photoaddition of Carvenone (1) to 1,1-Dimethoxyethylene. Formation of 11 and 12.—A solution of carvenone (500 mg) and 1,1-dimethoxyethylene (5 ml) in benzene (5 ml) was irradiated in a Pyrex tube for 10 hr. Removal of the solvent and the excess of olefin gave a light yellow liquid. Analysis by glpc showed two compounds, **11** and **12**, in relative ratio of 1:4, respectively. The liquid was chromatographed on basic alumina and elution with benzene gave **12** as a colorless oil (600 mg, 75%), which showed a single glpc peak. The oil was further purified by distillation, under reduced pressure, in a short-path distillation apparatus: ir (neat) 1685 cm^{-1}; nmr ($CDCl_3$) showed the bridgehead C-1 methine proton as a pair of doublets at δ 2.92 (J_1 = 8.5 and J_2 = 1 Hz, 1 H) and the methoxyl protons as a broad singlet at δ 4.1 (6 H).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.68; H, 10.22.

Hydrolysis of the Bicyclic Ketone 12 to Diketone 13.—A 100-mg portion of the ketone **12** in 1.5 ml of methanol was stirred, under nitrogen with 4 drops of concentrated hydrochloric acid in water (5 ml). After 2 days the reaction mixture was neutralized and extracted with chloroform to give **13** as a light yellow oil (70 mg, 88%). The infrared spectrum showed very strong absorption bands at 1780 (cyclobutanone) and 1710 cm^{-1} (cyclohexanone). The oil in methanol gave a negative ferric chloride test.

Photoaddition of Dimethyl Maleate to Carvenone. Formation of Diester 14.—A solution of carvenone (4 g, 0.027 mol) and dimethyl maleate (4 g, 0.027 mol) in diethyl ether (90 ml) was irradiated; the irradiation was stopped from time to time and ether was added to maintain the volume of the solution. After 30 hr the irradiation was stopped. Removal of the solvent under reduced pressure gave a colorless liquid, which showed on a tlc plate only one new spot, R_f 0.5 (hexane–ethyl acetate, 2:1), although glpc showed it to be a complex mixture. Repeated column chromatography on silica gave **14** as a thick liquid (800 mg, 10%): ir (neat) 1725 (ester C=O), 1705 (cyclohexyl C=O), 1387 and 1365 (isopropyl); nmr (CCl_4, 60 MHz) δ 0.7–1.4 (m, 11 H), 1.6–2.3 (m, 4 H), 2.8 (br, d, J = 10 Hz, 1 H, bridgehead cyclobutyl methine proton), 3.0–3.4 (m, 2 H), and 3.7 (s, 6 H); the 100-MHz nmr spectrum ($CDCl_3$) showed the bridgehead C-1 methine proton as a sharp doublet at δ 2.88 (J = 10 Hz), C-7 cyclobutyl proton as a sharp doublet at δ 3.52 (J = 3.5 Hz), C-8 methine proton as a multiplet at δ 3.2–3.5, and the methyl esters as a pair of singlets at δ 3.64 and 3.68; mass spectrum (70 eV) m/e (rel intensity) 296 (10, M^+, $C_{16}H_{24}O_5$ requires M^+, 296), 265 (20), 264 (32), 253 (5.6), 204 (40), 153 (16), 152 (94), 151 (24), 110 (100), 109 (26), 57 (17), 43 (28), and 41 (50).

(21) Determined with a Macrolab vapor pressure osmometer.

For analysis, the diester **14** was purified by preparative glpc. *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.87; H, 8.11. Found: C, 64.71; H, 8.34.

When the adduct **14** was heated under reflux with pyridine for 8 hr, only the starting material could be recovered (ir, nmr, and glpc analysis), showing the trans relationship of the ester groups and the cis fusion of the rings. The diester **14** was also recovered unchanged when allowed to stand in methanol containing sodium.

Photoaddition of Dimethyl Acetylenedicarboxylate to Carvenone. Formation of Diester 15.—The mixture of carvenone (3 g, 0.02 mol) and dimethyl acetylenedicarboxylate (5 g, 0.032 mol) was irradiated in a Pyrex tube for 30 hr. Analysis by tlc on silica (hexane–ethyl acetate, 2:1) as also by glpc showed the formation of only one product. The mixture was chromatographed on basic alumina and elution with benzene afforded the adduct **15** as a pale yellow liquid (750 mg, 12%): ir (neat) 1720 (ester C=O) and 1650 cm^{-1} (C=C); nmr ($CDCl_3$, 100 MHz) δ 0.94 (d, J = 6 Hz), 0.96 (d, J = 6 Hz), 1.1 (d, J = 7 Hz) (total 9 H), 1.46–2.6 (m, 6 H), 3.26 (s, 1 H, bridgehead methine proton), 3.74 (s) and 3.80 (s) (total 6 H); mass spectrum (70 eV) m/e (rel abundance) 294 (14, M^+, $C_{16}H_{22}O_5$ requires M^+, 294), 263 (17), 262 (23), 234 (30), 204 (67), 202 (25), 193 (20), 192 (46), 191 (33), 189 (24), 177 (25), 175 (26), 164 (33), 153 (11), 152 (40), 110 (50), 59 (55), 43 (43), and 41 (100). The analytical sample was obtained by further purification of **15** by preparative glpc.

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.31; H, 7.48. Found: C, 65.60; H, 7.63.

The unsaturated diester **15** was recovered unchanged when stirred with pyridine for 6 hr.

Photoaddition of 3-*tert*-Butyl-2-cyclohexenone (2) to Cyclohexene. Formation of 16 and 17.—A solution of 3-*tert*-butyl-2-cyclohexenone (2 g) and cyclohexene (5 ml) in benzene (5 ml) was irradiated in a Pyrex tube for 30 hr. Removal of the solvent and excess olefin under reduced pressure afforded a liquid, which showed two new glpc peaks. The liquid was chromatographed on neutral alumina and elution with *n*-hexane–benzene (1:1) gave **16** + **17** as a pale yellow liquid (1.15 g, 37%), with the same glpc retention times as in the crude photolysis mixture. The relative ratio of **16** and **17**, as found by glpc, was 5:1, respectively. The analytical sample was obtained as a thick, colorless liquid by distillation of the pale yellow liquid (short-path distillation at 0.05 mm in an oil bath at 80°).

Anal. Calcd for $C_{16}H_{26}O$ (mixture): C, 82.05; H, 11.11. Found: C, 82.22; H, 11.42.

The mixture was separated by preparative glpc. The major component **16** was a crystalline solid: mp 59–61°; ir (CCl_4) 1700, 1385, and 1360 cm^{-1}; nmr ($CDCl_3$, 100 MHz) δ 0.77 (s, 9 H), 1.2–2.2 (m, 16 H), and 2.42 (d, J = 9 Hz, 1 H, bridgehead C-2 methine proton).

The minor fraction **17** was obtained as a thick liquid: ir (CCl_4) 1695, 1388, and 1365 cm^{-1}; nmr ($CDCl_3$, 100 MHz) δ 0.75 (s, 9 H), 1.1–2.2 (m, 16 H), and 2.53 (d, J = 2.5 Hz, 1 H, bridgehead C-2 methine proton). The photoadducts were recovered unchanged when refluxed for 8 hr with pyridine.

Registry No.—**1**, 499-74-1; **2**, 17299-35-3; **3a**, 30462-49-8; **3a** 2,4-DNPH, 30462-50-1; **3b**, 31444-44-7; **3b** 2,4-DNPH, 31444-45-8; **4a**, 30462-51-2; **4a** 2,4-DNPH, 30462-52-3; **4b**, 31444-48-1; **4b** 2,4-DNPH, 31444-49-2; **5a**, 31444-50-5; **5a** bis-2,4-DNPH, 31489-90-4; **5b**, 31444-51-6; **5b** bis-2,4-DNPH, 31442-94-1; **8**, 31442-95-2; **9**, 31442-96-3; **10**, 31442-97-4; **12**, 31442-98-5; **13**, 31442-99-6; **14**, 31443-00-2; **15**, 31443-01-3; **16**, 31443-02-4; **17**, 31443-03-5.

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Concerning the Reaction of 1,3,5-Cyclooctatrien-7-yne at Various Temperatures

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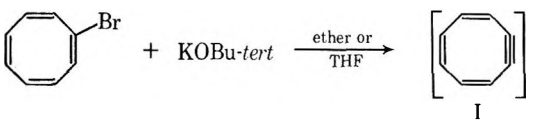
1,3,5-Cyclooctatrien-7-yne (dehydrocyclooctatetraene) has been reported to be best prepared in ether at room temperature to afford the highest yield of adduct with a trapping agent. We now report on how the yields of product from the reaction of this species with a trapping agent vary depending upon (a) when the trapping agent is added and (b) the temperature employed. Our results indicate that, contrary to previous indicated reports, dehydrocyclooctatetraene is best prepared and allowed to react at temperatures other than room temperature.

The recently[1,2] prepared 1,3,5-cyclooctatrien-7-yne (dehydrocyclooctatetraene, I) has been reported[2] to be best prepared in ether at room temperature to afford the highest yield of adduct with a trapping agent. We now report on how the yields of product, from the reaction of this species with a trapping agent, vary depending upon (a) when the trapping agent is added and (b) the temperature employed. Our results indicate that, contrary to previous indicated reports, I is best prepared and allowed to react at temperatures other than room temperature.

The method used[1,2] to prepare I is treatment of bromocyclooctatetraene with potassium *tert*-butoxide at room temperature in ether or tetrahydrofuran



I

(THF). In the absence of any trapping agent, I has been observed[1,2] to react with the base to yield *tert*-butoxycyclooctatetraene or to dimerize to cycloocta-[*b*]naphthalene. The intermediate I may, however, be trapped with a variety of trapping agents (*e.g.*, 1,3-diphenylisobenzofuran,[1,2] phenyl azide,[1,2] 1-diethylaminobutadiene,[1,2] and furan[3]), but tetraphenylcyclopentadienone (tetracyclone) was chosen for this study because of its availability and because of the high

(1) A. Krebs, *Angew. Chem., Int. Ed. Engl.*, **4**, 953 (1965).
(2) A. Krebs and D. Byrd, *Justus Liebigs Ann. Chem.*, **707**, 66 (1967).
(3) A. Krebs, personal communication reported in R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, 1967, p 349.

TABLE I

YIELD OF PRODUCT AT 25.0 ± 0.1° WITH ELAPSED TIME BEFORE TETRACYCLONE ADDITION

Time, min	0.0	5.0	15.0	30.0
Yield, %[a]	20.5 ± 0.1	14.3 ± 0.1	8.1 ± 0.1	5.7 ± 0.1
Time, min	45.0	60.0	90.0	120.0
Yield, %[a]	3.0 ± 0.1	1.7 ± 0.1	0.9 ± 0.2	Trace

[a] Average of quintuplicate runs.

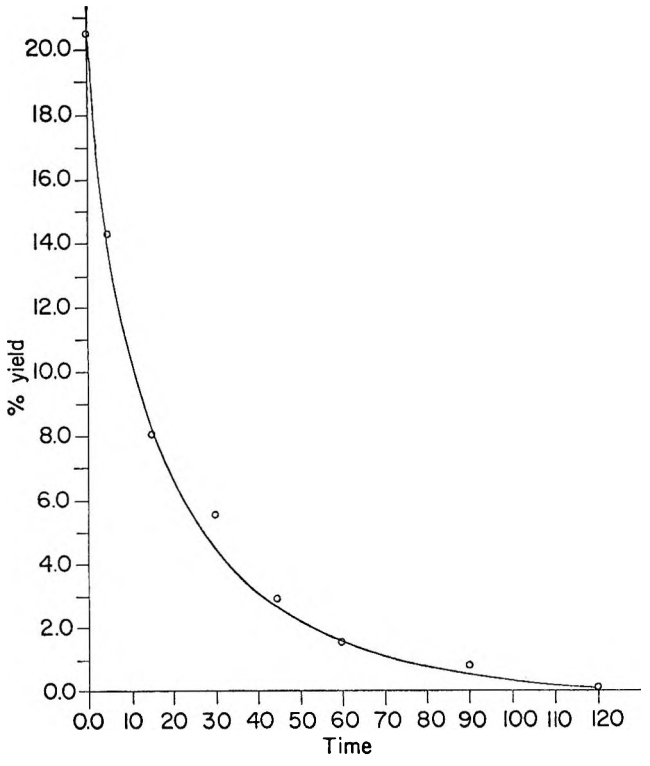
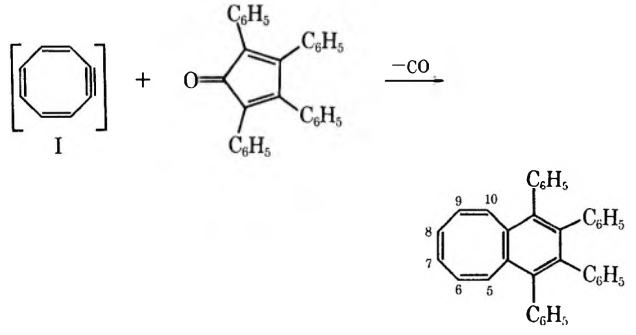


Figure 1.—Reaction of 1,3,5-cyclooctatrien-7-yne with tetracyclone. The yields are the average of quintuplicate runs. Time indicates number of minutes elapsing between introduction of bromocyclooctatetraene and introduction of tetracyclone.

yield[1,2] of 1,2,3,4-tetraphenylbenzocyclooctatetraene obtained by the Diels–Alder reaction of I with tetracyclone.



Preparation of I was accomplished under high vacuum in a specially constructed flask which allowed introduction of the tetracyclone, under vacuum, to the reaction mixture at different time intervals after the formation of I had begun; the mixture was allowed to stir[4] for exactly 30 min and the 1,2,3,4-tetraphenylbenzocyclooctatetraene was isolated. This method gives an indication of the optimum time to introduce a trapping agent to react with I. Using this procedure, the best results at room temperature (25.0 ± 0.1°) were obtained when the tetracyclone was present initially, and the yields of product dropped rapidly with even a 5-min time lapse before the trapping agent was added. These results indicate that I is very reactive and if a trapping agent is not available for immediate reaction, the dehydrocyclooctatetraene disappears by reacting with itself and/or the base. The results of this study (Table I and Figure 1) are presented as the per cent yield of product obtained when the given number of minutes were allowed to elapse between the initiation of the dehydrocyclooctatetraene formation and the introduction of tetracyclone. These results are reasonable in light of similar experiments performed with cycloheptyne and cyclohexyne.[5]

In order to obtain information on what competing reactions are possible for the dehydrocyclooctatetraene once it is formed, all material was recovered and examined for three runs at *t* 30.0. In addition to the 1,2,3,4-tetraphenylbenzocyclooctatetraene and unreacted tetracyclone, the only other products present to any extent were *tert*-butoxycyclooctatetraene and cycloocta-[*b*]naphthalene. Thus it appears that besides Diels–Alder reaction with the trapping agent, dimerization and reaction with base are the only other competing pathways for the dehydrocyclooctatetraene.

Once it had been established that the best yields at room temperature were obtained when the trapping agent is present initially, we turned our attention to the effect of temperature. When the reaction between I and tetracyclone is performed under vacuum at 30.0 ± 0.1° in ether with the tetracyclone present initially, the yields of product are increased by more than 50% above the yields obtained at room temperature (Table II). However, when the reaction is performed under vacuum at 0.0 ± 0.1° in ether with the tetracyclone present initially, the yields of product are again increased over room temperature, although not so greatly. These results are presented in Table II where they are compared with the runs at room temperature with the tetracyclone present initially. Evidently two opposing factors are in effect with the temperature change. An increase in reaction rate with increased temperature is the expected kinetic result, and this seems to explain the increased yields of product when the reaction is run at the higher temperature. The intermediate I is highly reactive, however, and apparently lower temperatures prolong the lifetime of this species signifi-

TABLE II

YIELDS OF PRODUCT AT VARIOUS TEMPERATURES WITH TETRACYCLONE PRESENT INITIALLY

Temp, °C	30.0 ± 0.1	25.0 ± 0.1	0.0 ± 0.1
Yield, %[a]	37.4 ± 0.1	20.5 ± 0.1	26.2 ± 0.1

[a] Average of quintuplicate runs.

(4) Changing the rate of stirring had little effect upon the yield.

(5) J. Schüller, Ph.D. Thesis, University of Heidelberg, 1966, reported in "Dehydrobenzene and Cycloalkynes," ref 3, pp 356, 357.

cantly. In order to establish this, rate studies[6] were also performed at 0.0 ± 0.1°, and the results are recorded below in Table III.

TABLE III
YIELD OF PRODUCT AT 0.0 ± 0.1° WITH ELAPSED TIME BEFORE TETRACYCLONE ADDITION

Time, min	0.0	5.0	15.0
Yield, %[a]	26.2 ± 0.1	19.8 ± 0.1	11.4 ± 0.1

[a] Average of quintuplicate runs.

If these results are compared with the results obtained for the room-temperature (25.0 ± 0.1°) kinetic study, it can be seen that the yields of product are consistently higher for the low-temperature reactions. Therefore, it appears that at lower temperatures the intermediate is less apt to react with itself or the base before colliding fruitfully with a tetracyclone molecule. Thus, room temperature appears to be a low point on the temperature–yield curve generated by these two opposing trends. One possible explanation for these results is that, since dimerization and reaction of I with the base are the only other competing reactions observed for the dehydrocyclooctatetraene, we may consider the reaction between I and tetracyclone to have a lower energy of activation than either of the above competing side reactions, at the lower temperature. Thus the increase in yields at the lower temperature is probably due to a decrease in the rate of formation of the side products, and as a consequence more dehydrocyclooctatetraene is available for reaction with the tetracyclone.

In order to obtain an indication of the effect of time on the yields of product from the reaction of I with tetracyclone, three room-temperature (25.0 ± 0.1°) reactions and three reactions at 30.0 ± 0.1°, all under vacuum and with the tetracyclone present initially, were allowed to run to essential completion. After 70 hr, the yield of 1,2,3,4-tetraphenylbenzocyclooctatetraene obtained from the room-temperature reactions was 79.9 ± 0.1% which corresponds closely to the 72% yield which Krebs obtained[1,2] with no special precautions. However, after the same length of time, the yield of 1,2,3,4-tetraphenylbenzocyclooctatetraene obtained from the higher temperature reactions was 90.9 ± 0.1%. Allowing other reactions to proceed for longer than 70 hr did not increase the yield of product.

Thus the yield of product from the reaction of I with tetracyclone is maximized at 91% if the reaction is performed under vacuum, in ether at 30° with the trapping agent present initially.

Experimental Section

Bromocyclooctatetraene-1,3,5,7.—The preparation of bromocyclooctatetraene was based on the method of Konz and Huisgen[7] and Sargent.[8] Into a 1-l. flask equipped with a mechanical stirrer, dropping funnel, condenser, and nitrogen inlet was placed, under nitrogen, a solution of 52 g (0.5 mole) of freshly distilled cyclooctatetraene in 350 ml of methylene chloride (distilled from phosphorus pentoxide), and the mixture was cooled with a Dry Ice–acetone bath to −60 to −65°. Then within 1 hr, 82 g (1.0 mol) of bromine in 150 ml of absolute methylene chloride was added dropwise with strong stirring. The solution was continuously stirred at −60° for 1 hr, and then 80 g (0.71 mol) of potassium *tert*-butoxide was added in 5- to 10-g portions while the temperature was maintained at −55 to −60°. When addition of the potassium *tert*-butoxide was complete, the solution was stirred at −60° for an additional hour. During the addition, the mixture was strongly stirred and the nitrogen stream increased. The temperature was then raised to −50 to −45°, and the mixture was stirred for 3 hr at this temperature. Then the temperature was raised to −10° within 1 hr and the reaction mixture poured into 750 ml of water and 12.5 ml of acetic acid. The emulsion which formed was treated with 25 g of magnesium sulfate, and a clear phase separated. The organic phase was separated and the aqueous layer saturated with sodium chloride and extracted with a total of 750 ml of ether in three portions. The combined extracts were washed with three 300-ml portions of water, two 300-ml portions of 5% sodium bicarbonate solution, and again with water (one 300-ml portion) and dried over magnesium sulfate. Removing the solvent at room temperature afforded a residue which was then distilled under vacuum. The bromocyclooctatetraene distilled at 26–28° (2×10^{-6} mm): yield 70 g (0.38 mol, 76%); nmr (neat) τ 4.5 (m, 7).

Reaction of I with Tetracyclone at Room Temperature for 70 Hr.—Approximately 200 ml of anhydrous ether was allowed to stand over Na–K alloy on the vacuum line, degassed twice, and then distilled onto fresh Na–K alloy. For the reaction a specially designed flask was used which had a side arm with a 2-ml bulb to hold the bromocyclooctatetraene. After this flask had been flamed and flushed with nitrogen, 1.83 g (0.01 mol) of bromocyclooctatetraene was placed in the side-arm bulb which was then sealed. Potassium *tert*-butoxide (1.12 g, 0.01 mol) and 3.84 g (0.01 mol) of tetracyclone were placed in the bottom of the flask along with a magnetic stirring bar; the flask was immediately placed on the vacuum line and evacuated for a few minutes, and the potassium *tert*-butoxide was heated gently and briefly with a heat gun to remove any moisture present. The ether was then distilled into the flask and the flask sealed at the neck. The ether was allowed to warm to room temperature (25.0 ± 0.1°) in a thermostatically controlled constant temperature bath and the flask tilted to introduce the bromocyclooctatetraene. The flask was kept in the constant-temperature bath and the mixture allowed to react with stirring for 70 hr; the flask was opened and the mixture transferred to a separatory funnel and washed with 100 ml of water. This water wash was separated and washed with 100 ml of ether, and the ether was added to the original mixture. The combined ether solutions were washed successively with 150-ml portions of water until the wash water was clear (only one wash usually required), 150 ml of 10% HCl, and twice more with 150 ml of water. The solution was dried over anhydrous magnesium sulfate, the ether evaporated, and the residue dissolved in carbon tetrachloride and chromatographed on a 45 cm × 4.5 cm silica gel column using carbon tetrachloride as eluent. Evaporation of the carbon tetrachloride afforded a white crystalline material which was recrystallized from glacial acetic acid: yields for the three separate runs were 3.66, 3.67, and 3.67 g (0.0079 and 0.0080 mol, 79.9 ± 0.1%); mp 246° (lit.[2] 241–242°); nmr (CCl_4) τ 2.81–3.31 (A_2B_2 multiplet, 20, ArH), 3.70 and 4.12 (doublet of AB quartet, 2, vinyl adjacent to benzo ring $H_{5,10}$), and 3.92 and 4.30 (high-field doublet of AB quartet superimposed on a singlet at 3.92, 2, vinyl $H_{6,9}$; 2, vinyl $H_{7,8}$).

Anal. Calcd for $C_{36}H_{26}$: C, 94.29; H, 5.71. Found: C, 93.98; H, 5.80.

Reaction of I with Tetracyclone at 30° for 70 Hr.—The reaction as described above using the same proportions of reactants was carried out with the tetracyclone present initially (t 0.0); the temperature was maintained at 30.0 ± 0.1° by a thermostatically controlled constant-temperature bath for the entire reaction time of 70 hr. The yields for the three separate runs were 4.16, 4.17, and 4.18 g (0.0091, 0.0091, and 0.0091 mol, 90.9 ± 0.1%).

Room-Temperature Kinetic Study of the Reaction of I with Tetracyclone.—The kinetic study was performed by setting up the reaction in the manner described below, but allowing various time intervals to elapse between the addition of bromocyclooctatetraene and the addition of tetracyclone. The ether was prepared in the same manner as described above. The reaction vessel used throughout this study consisted of a specially designed 500-ml flask which had two side arms; one side arm had

(6) We thank the referees for suggesting this study.
(7) R. Huisgen, private communication.
(8) M. V. Sargent, private communication.

a 2-ml bulb to hold the bromocyclooctatetraene, while the other side arm had a larger bulb to hold the tetracyclone. The tetracyclone (3.86 g, 0.01 mol) was placed in the larger bulb and the bulb sealed, except for the *t* 0.0 runs when the tetracyclone was placed in the bottom of the flask. The bromocyclooctatetraene (1.83 g, 0.01 mol) was placed in the smaller bulb which was also sealed. The potassium *tert*-butoxide (1.12 g, 0.01 mol) was placed in the bottom of the flask along with a magnetic stirring bar[4] and the flask immediately placed on the vacuum line and evacuated. The potassium *tert*-butoxide was heated briefly and gently with a heat gun, the flask allowed to cool, and the ether distilled over. The flask was sealed at the neck and placed in a thermostatically controlled constant-temperature bath at 25.0 ± 0.1°, and then the bromocyclooctatetraene was added to the potassium *tert*-butoxide–ether solution. The bromocyclooctatetraene was allowed to react with the base for the prescribed length of time as indicated in Table I; then the tetracyclone was introduced; and the mixture allowed to react for exactly 30 min. The flask was opened and the mixture treated as above. The results obtained were (*t* 0.0) one yield of 0.93 g (20.3%), two of 0.94 g (20.5%), and two of 0.95 g (20.7%); (*t* 5.0) two yields of 0.65 g (14.2%) and three of 0.66 g (14.4%); (*t* 15.0) two yields of 0.37 g (8.1%) and three of 0.38 g (8.3%); (*t* 30.0) one yield of 0.25 g (5.5%), two of 0.26 g (5.7%), and two of 0.27 g (5.9%); (*t* 45.0) one yield of 0.13 g (2.8%) and four of 0.14 g (3.1%); (*t* 60.0) two yields of 0.07 g (1.5%), two of 0.08 g (1.7%), and one of 0.09 (2.0%); (*t* 90.0) two yields of 0.03 g (0.7%), one of 0.04 g (0.9%), and two of 0.05 g (1.1%); (*t* 120.0) only trace amounts were obtained in all five cases. For three runs at *t* 30.0, all material was recovered and examined. The product (0.25, 0.26 and 0.26 g, 0.054 and 0.057 mol, 5.4 and 5.7%) and the unreacted tetracyclone (3.10, 3.10, and 3.12 g, 0.806 and 0.811 mol, 80.6 and 81.1%) were eluted from the chromatography column with carbon tetrachloride (the product is eluted first), and then the column was stripped by elution with acetone. Evaporation of the acetone and tlc on a silica gel plate using 3:1 carbon tetrachloride–acetone showed two main bands and a number of lesser ones. The two main bands were separately extracted, filtered, and subjected to nmr and mass spectroscopy; they proved to be *tert*-butoxycyclooctatetraene[2] and cycloocta[*b*]-naphthalene.[3]

Various Temperature Kinetic Studies of the Reaction of I with Tetracyclone.—The reaction as described above using the same proportions of reactants was carried out with the tetracyclone present initially (*t* 0.0) but keeping the reaction mixture at the temperatures indicated below for the reaction period of 30 min. Quintuplicate runs were made with the temperature maintained at 30.0 ± 0.1° (just below the reflux temperature of ether) by means of a thermostatically controlled constant-temperature bath. Yields for this reaction were three of 1.71 g (37.3%) and two at 1.72 g (37.5%). On a separate set of determinations the reaction mixture was kept in a thermostatically controlled constant-temperature bath at 0.0 ± 0.1° for the 30-min reaction period. Yields for this reaction were three of 1.20 g (26.2%) and two of 1.21 g (26.4%).

Low-Temperature Kinetic Study of the Reaction of I with Tetracyclone.—The reaction as described above using the same proportions of reactants was carried out with the temperature of the thermostatically controlled constant-temperature bath maintained at 0.0 ± 0.1°, adding the tetracyclone at different time intervals after the bromocyclooctatetraene was added to the base and allowing the reaction to proceed after the addition of the tetracyclone for exactly 30 min. The results obtained were (*t* 0.0) three yields of 1.20 g (26.2%) and two of 1.21 g (26.4%); (*t* 5.0) one yield of 0.90 g (19.6%), three of 0.91 g (19.8%), and one of 0.92 g (20.0%); (*t* 15.0) one yield of 0.51 g (11.1%), two of 0.52 g (11.3%), and two of 0.52 g (11.6%).

Registry No.—I, 4514-69-6; tetracyclone, 479-33-4; bromocyclooctatetraene-1,3,5,7, 7567-22-8; 1,2,3,4-tetraphenylbenzocyclooctatetraene, 4514-72-1.

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Friedel–Crafts Cyclialkylations and Bicyclialkylations with Diphenylalkyl Chlorides[1]

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Cyclialkylation of 1-chloro-4,5-diphenylpentane (**1a**) by $AlCl_3$ produced 1-benzyltetralin (**2a**) and no 2-phenylbenzosuberane, showing the preference of six-ring formation over seven-ring formation. No products expected to result from initial rearrangement of the primary chloride to a secondary carbonium ion preceding cyclialkylation were found, *e.g.*, no 1-benzyl-3-methylindan or 1-methyl-3-phenyltetralin. A second major product was found to be 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**10a**), which is formed from **2a** by hydride abstraction and bicyclialkylation. Similar treatment of 1-chloro-2-methyl-4,5-diphenylpentane (**1b**) with $AlCl_3$ gave 1-benzyl-3-methyltetralin (**2b**) and 1-methyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**10b**); more extensive bicyclialkylation of **2b** to **10b** was found, in line with the greater ease of abstraction of a tertiary hydride ion from **2b**. Two other products from **1b** were 1-benzyl-3,3-dimethylindan (**7b**) and 1,1-dimethyl-3-phenyltetralin (**8b**), resulting from initial rearrangement of the primary chloride to a tertiary carbonium ion preceding cyclialkylation.

In an earlier publication[3] we described the cyclialkylation of 1-chloro-3,4-diphenylbutane to yield 2-phenyltetralin as the almost-exclusive product, thus demonstrating the preference for six-membered ring (tetralin) formation over five-membered ring (indan) formation, either directly or *via* rearrangement to a secondary carbonium ion intermediate. We remarked then that interesting tests for competing direct cyclialkylations and those involving rearrangements of primary phenylalkyl chlorides to secondary and tertiary carbonium ion intermediates would be provided by studies of reactions of 1-chloro-4,5-diphenylpentane (**1a**) and 1-chloro-2-methyl-4,5-diphenylpentane (**1b**) with aluminum chloride. The present paper describes such studies.

Possible cyclialkylations, and rearrangements followed by cyclialkylations, of these phenylalkyl chlorides are outlined in Scheme I. The numbers over the arrows refer to the ring size produced in the cyclialkylation step.

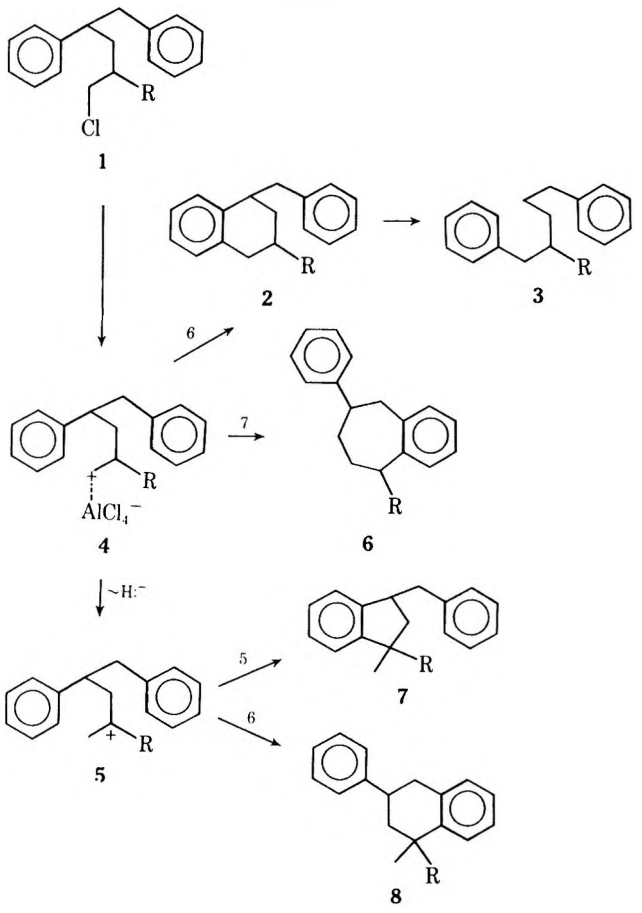
Treatment of 1-chloro-4,5-diphenylpentane (**1a**) with aluminum chloride in petroleum ether or carbon di-

(1) (a) Part XXV of the series, "New Friedel-Crafts Chemistry." Part XXIV: A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **36**, 1040 (1971). (b) Generous support of this research, including a postdoctoral fellowship for A. A. Khalaf, by the Robert A. Welch Foundation, is gratefully acknowledged.

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

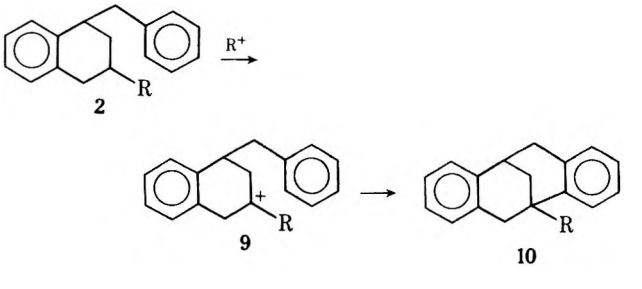
(3) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **31**, 89 (1966).

SCHEME I



a series, R = H
b series, R = Me

sulfide solution at room temperature gave 1-benzyltetralin (**2a**) as the major product and some 1,5-diphenylpentane (**3a**), presumably formed from **2a** by dealkylation at the tertiary carbon, followed by hydride exchange (Table I). No 2-phenylbenzosuberane (**6a**), 1-benzyl-3-methylindan (**7a**), or 1-methyl-3-phenyltetralin (**8a**) could be detected, but another product was identified as 2,3:6,7-dibenzobicyclo [3.3.1]nona-2,6-diene (**10a**). This is produced from 1-benzyltetralin (**2a**) by hydride abstraction followed by bicyclialkylation (**2a** → **9a** → **10a**). When



a series, R = H
b series, R = Me

the reaction was carried out in petroleum ether at 70° for 2.5 hr, the amount of **2a** decreased and the amount of **10a** increased, as did also the amount of 1,5-diphenylpentane. No **6a**, **7a**, or **8a** were produced, however.

Treatment of 1-chloro-2-methyl-4,5-diphenylpentane (**1b**) with aluminum chloride in petroleum ether or carbon disulfide at room temperature gave a more complex mixture of products, including 1-benzyl-3-methyltetralin (**2b**), 1-benzyl-3,3-dimethylindan (**7b**), 1,1-dimethyl-3-phenyltetralin (**8b**), 1-methyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**10b**), and 2-methyl-1,5-diphenylpentane (**3b**, Table I). No 1-methyl-4-phenylbenzosuberane (**6b**) could be detected. The ratio of **10b**/**2b** was much higher than the ratio of **10a**/**2a** produced under similar reaction conditions, reflecting the greater ease of abstracting a hydride ion from the tertiary C-3 carbon of **2b** than from the corresponding secondary carbon of **2a**. The formation of the rearranged cyclialkylation products **7b** and **8b** may also be attributed to the greater driving force for rearrangement of the intermediate primary complex **4b** to the tertiary carbonium ion **5b**, rather than to the secondary carbonium ion **5a**. The more facile formation of a five-membered ring by an intermediate tertiary carbonium ion is also a factor; this has been noted before.[3]

The intermediacy of **2a** and **2b** in the formation of **10a** and **10b** from **1a** and **1b** was confirmed by treating **2a** and **2b** separately with aluminum chloride. The major products, as expected, were as follows: from **2a**, **10a** and **3a**; from **2b**, **10b** and **3b**. No products corresponding to structures **7** and **8** were found.

The 1-chloro-2-methyl-4,5-diphenylpentane (**1b**) used as starting material in the cyclialkylations and bicyclialkylations reported here was a mixture of diastereomers. In order to examine the possibly different behaviors of the individual diastereomers toward cyclialkylation and bicyclialkylation, we have obtained them, as well as the individual diastereoisomeric benzyl tetralins (**9b**), by stereoselective syntheses. The results from these investigations will be reported subsequently.

Experimental Section[4]

1-Chloro-4,5-diphenylpentane (**1a**).—γ-Chlorobutyrophenone (Aldrich) was treated with benzylmagnesium chloride in dry ether. The reaction mixture was worked up in the usual way and the crude product alcohol was catalytically hydrogenated at low pressure with Pd/C in glacial acetic acid containing perchloric acid to give the title compound: bp 164–165° (2 mm); n^{25}D 1.5572; mass spectrum (70 eV) m/e 258–260 molecular ion; ir compatible with the structure; nmr (CCl_4) δ 1.3–1.8 (m, 4 H, CH_2CH_2), 2.75 [broad s, 3 H, $PhCH_2CH(Ph)$], 3.15 (t, 2 H, J = 7 Hz, CH_2Cl), and 6.8–7.2 ppm (m, 10 H, aromatic); mass, calcd for $C_{17}H_{19}{}^{35}Cl$, 258.1175 (found, 258.1170).

1-Chloro-2-methyl-4,5-diphenylpentane (**1b**).—2-Methyl-4,5-diphenylpent-1-ene-5-one was prepared from deoxybenzoin and methallyl chloride by a known procedure[5] and reduced by a modified[3] Wolff–Kishner method to 2-methyl-4,5-diphenylpent-1-ene. Hydroboration, followed by treatment with NaOH–H_2O_2,[6] gave 2-methyl-4,5-diphenylpentan-1-ol: bp 156–170° (0.6 mm); n^{25}D 1.5580 (a mixture of diastereomers); nmr (CCl_4) δ 0.55–0.85 (m, 3 H, CH_3), 1.1–1.9 [m, 3 H, $CH_2CH(CH_3)$], 2.65–2.85 [broad s, 3 H, $PhCH_2CH(Ph)$], and 2.95–3.25 ppm (m, 3 H, CH_2OH) (the breadth of the peaks is attributable to

(4) Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. and by A. Bernhardt, Mülheim, Germany. The nmr spectra were determined in CCl_4 on a Varian A-60 instrument with TMS as internal standard. Analytical glpc was performed using a Varian Hy-Fi Model 600-D instrument; preparative glpc separations were made with a Wilkens A-700 (Autoprep) instrument. Infrared spectra were recorded on a Beckman IR-5A instrument.

(5) C. M. Suter and A. W. Weston, *J. Amer. Chem. Soc.*, **64**, 534 (1942).

(6) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6433 (1955).

TABLE I

PRODUCTS FROM CYCLIALKYLATION AND BICYCLIALKYLATION OF DIPHENYLALKYL CHLORIDES WITH ALUMINUM CHLORIDE[a]

Diphenylalkyl chloride	Solvent	Temp, °C	Time, hr	Products, %[b] 2a	3a	7a	8a	10a
1-Chloro-4,5-diphenylpentane (1a)	Petroleum ether[c]	25	2.5	47	36	0	0	15
	Petroleum ether[c]	70	1.0	21	51	0	0	27
	CS_2[c]	25	2.5	76	12	0	0	10
				2b	3b	7b	8b	10b
1-Chloro-2-methyl-4,5-diphenylpentane (1b)	Petroleum ether[d]	25	2.5	9	10	16	19	39
	CS_2[e]	25	2.5	(5)[f]	11	26	(12)[f]	38

[a] Reactants proportions, RCl-$AlCl_3$-solvent = 1 g:0.25 g:5 ml. [b] Relative amounts of products distilling in the diphenylalkane range; about 50% of reaction products were in the monophenylalkane range, owing to dephenylation. The relative amounts were determined by glpc; totals do not add up to 100% because small amounts of known and unidentified products are not included in the table. [c] Glpc analysis: 8 ft × 0.25 in. XF-1165 (30%) on 60–80 mesh Chromosorb W column operated at 230–240° with helium carrier gas at 120 cc/in. [d] Glpc analysis: 16 ft × 0.125 in. DEGA (25%) on 45–60 mesh Chromosorb W column operated at 210° with nitrogen carrier gas at 30 psi. [e] Glpc analysis: 6 ft × 0.25 in. SE-30 silicone gum rubber on 42–60 mesh firebrick column operated at 220° with helium carrier gas at 40 psi. [f] These two products were not resolved by the glpc analysis; the proportion is assumed to be similar to that found in the reaction carried out in petroleum ether, where resolution was successful.

the presence of both diastereomers); ir (neat) 3330 cm^{-1} (broad, OH). The mass spectrum (70 eV) showed no parent peak.

Anal. Calcd for $C_{18}H_{22}O$: C, 85.04; H, 8.66; O, 6.30. Found: C, 84.80; H, 8.54; O, 6.42.

The alcohol was converted to the title compound using a 2:1 molar ratio of thionyl chloride in pyridine, refluxing at 100° for 1 hr: bp 172–174° (1.5 mm); nmr (CCl_4) δ 0.6–0.9 (m, 3 H, CH_3), 1.1–1.9 [m, 3 H, $CH_2CH(CH_3)$], 2.6–2.9 [broad s, 3 H, $PhCH_2CH(Ph)$], and 3.0–3.3 ppm (m, 2 H, CH_2Cl) (the breadth of the peaks is attributable to the presence of both diastereomers); mass spectrum (70 eV) *m/e* 272–274 molecular ion (weak).

Anal. Calcd for $C_{18}H_{21}Cl$: Cl, 12.99. Found: Cl, 12.67.

Reaction of the Diphenylalkyl Chlorides with Aluminum Chloride.—The diphenylalkyl chlorides, dissolved in petroleum ether (bp 60–70°) or carbon disulfide, were added dropwise to anhydrous aluminum chloride suspended in the same solvent. The mixtures were stirred magnetically in a flask to which was attached a reflux condenser protected by a calcium chloride drying tube, either at room temperature for 2.5 hr or, in some experiments with petroleum ether as solvent, at reflux for 1 hr. The proportions of the diphenylalkyl chlorides–$AlCl_3$–solvent were 1 g:0.25 g:5 ml. The reaction mixtures were decomposed with water and worked up in the usual way. The hydrocarbon products were distilled and analyzed by glpc (see Table I).

The bicyclialkylation product, 2,3:6,7-dibenzobicyclo[3.3.1]-nona-2,6-diene (10a), was isolated by preparative glpc, using an 8 ft × 0.25 in. XF-1165 column operated at 230–240° with helium carrier gas at a rate of 120 cc/min, mp 73.5–75° (lit.[7] mp 78°). It was identical with the product obtained by cyclialkylation of 1-benzyltetralin as described below.

The homologous product 10b was isolated from the bicyclialkylation reaction of 1b (20 g) carried out in carbon disulfide (Table I). After decomposition of the reaction mixture with water in the usual way, the organic products were distilled and the fraction, 4.5 g, bp 145–154° (0.5–1.0 mm), was subjected to chromatography on a 110 × 3 cm column of silica gel (E. Merck, type G, pH 7), eluting with pentane. The white crystalline material obtained from the middle elution fractions was sublimed *in vacuo* to yield 1.3 g of 1-methyl-2,3:6,7-dibenzobicyclo-[3.3.1]nona-2,6-diene (10b) as white, fluffy crystals: mp 86.5–89°; nmr (CCl_4) δ 1.48 (s, 3 H, CH_3), 1.8–2.0 (broad, spiked s, 2 H, bridge CH_2), 2.5–3.5 (m, 5 H, benzylic), and 6.7–7.4 ppm (m, 8 H, aromatic); mass spectrum (70 eV) *m/e* 234 (molecular ion), 219 (base peak).

Anal. Calcd for $C_{18}H_{18}$: C, 92.31; H, 7.69. Found: C, 92.33; H, 7.71.

This product was identical with the product obtained by cyclialkylation of 1-benzyl-3-methyltetralin as described below and with the product obtained by sulfuric acid catalyzed dehydration of 4-benzyl-2-methyl-1-tetralol, in work which will be reported separately.

1-Benzyltetralin (2a).—α-Tetralone (Aldrich) was treated with benzylmagnesium chloride in dry ether. The crude carbinol was hydrogenated at low pressure with Pd/C catalyst in glacial acetic acid containing perchloric acid. The title compound had bp 143–144° (1.4 mm), $n^{25}D$ 1.5813 [lit.[8] bp 145–146° (0.6 mm)]; ir, nmr, and mass spectra were all consistent with the title formulation.

1-Benzyl-3-methyltetralin (2b).—3-Methyl-1-tetralone was synthesized starting with phenylacetone and ethyl bromoacetate as described in the literature:[9] bp 67–68° (0.17 mm) [lit.[9b] bp 132–136° (14 mm)]; $n^{24}D$ 1.5562; ir (film) 1690 cm^{-1} (C=O); nmr (CCl_4) δ 1.03 (d, 3 H, J = 7.0 Hz, CH_3), 1.90–3.00 (cluster of multiplets, 5 H, all other nonaromatic), 7.00–7.50 and 7.80–7.98 ppm (both multiplets, 3 H and 1 H, respectively, aromatic).

Reaction of the latter ketone with benzylmagnesium chloride followed by hydrogenation of the resulting 1-benzyl-3-methyl-1-tetralol with hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid[10a] gave the desired 1-benzyl-3-methyltetralin: bp 115–116° (0.2 mm); $n^{23}D$ 1.5694; nmr (CCl_4) δ 0.92 and 0.98 (both doublets in a ratio of 4:1 totaled 3 H, J = 6.8 Hz, CH_3), 1.25–3.45 (unresolved, 8 H, all other nonaromatic), and 6.90–7.30 ppm (m with sharp singlet at 7.12, 9 H, aromatic).

Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.29; H, 8.61.

It is to be noted that both glpc and nmr analysis showed the latter hydrocarbon to be a mixture of two diastereomers[10b] in a ratio of about 4:1.

Bicyclialkylation of 1-Benzyltetralin and 1-Benzyl-3-methyltetralin with Aluminum Chloride.—To 5 mmol of the hydrocarbon in 10 ml of carbon disulfide was added 2.5 mmol of anhydrous $AlCl_3$, and the mixture was stirred magnetically at room temperature. After various time intervals, 0.5-ml samples of the solution were withdrawn by pipet and analyzed by glpc.[11] After 56 hr, conversion of both tetralins was about 90% complete. The products were as follows: from 1-benzyltetralin, 10a (80%), 3a (20%); from 1-benzyl-3-methyltetralin, 10b (78%), 3b (22%).

Synthesis of Authentic Compounds for Comparison or Identification with Products of Cyclialkylations and Bicyclialkylations. 2,3:6,7-Dibenzobicyclo[3.3.1]nona-2,3-diene (10a) was synthesized by the procedure of Stetter and Reischl,[7] starting with α,γ-diphenylglutaric acid. In the second step, the reduction of the diketone was accomplished in better yield (90%) by catalytic hydrogenation using 5% Pd/C in glacial acetic acid containing perchloric acid,[10a] rather than by Wolff–Kishner reduction (56.6% yield reported[7]). Our product had mp 74–76° (lit.[7] mp 78°); its ir and nmr spectra were consistent with the assigned structure.

(7) H. Stetter and A. Reischl, *Chem. Ber.*, **93**, 791 (1960).

(8) H. Beyer and H. Schulte, *Ber.*, **74B**, 98 (1941).

(9) (a) S. Natelson and S. P. Gottfried, *J. Amer. Chem. Soc.*, **61**, 970 (1939); (b) F. Weygand and K. Schroder, *Ber.*, **74**, 1844 (1941).

(10) (a) R. M. Roberts, G. A. Ropp, and O. K. Neville, *J. Amer. Chem. Soc.*, **77**, 1764 (1955). (b) These two diastereomers were synthesized by R. M. Roberts and K.-H. Bantel using a sequence of standard procedures which will be published separately.

(11) Products from 1-benzyltetralin were analyzed on a 5 ft × 0.125 in. SE-30 silicone gum rubber (5%) on 42–60 mesh firebrick column operated at 220° with nitrogen carrier gas at 5 psi. Products from 1-benzyl-3-methyltetralin were analyzed on a 10 ft × 0.125 in. Bentone-34 (5%) and SE-52 (5%) on Chromosorb W column operated at 210° with nitrogen carrier gas at 60 psi.

1,5-Diphenylpentane (**3a**) was prepared by reaction of 4-phenylbutylmagnesium bromide with benzaldehyde, followed by catalytic hydrogenolysis of the carbinol,[10a] bp 83–87° (0.1 mm) (lit.[12] bp 190–192°). The product was purified by preparative glpc (16 ft × 0.25 in. 30% XF-1150 column with helium carrier gas at 190°, 40 psi); the ir and nmr spectra were consistent with the assigned structure.

2-Methyl-1,5-diphenylpentane (**3b**) was synthesized starting with phenylacetone and 3-phenylpropylmagnesium bromide. The 2-benzyl-5-phenyl-2-pentanol so obtained had bp 110° (0.12 mm) and ir and nmr spectra consistent with its formulation. The alcohol was dehydrated by means of pyridine and phosphorus oxychloride,[13] and the mixture of alkene isomers was catalytically hydrogenated as before[10a] to give the title hydrocarbon, bp 102–108° (0.14 mm). It was purified by preparative glpc (16 ft × 0.25 in. 30% XF-1150 column with helium carrier gas at 190°, 40 psi): ir (film) 3080 (m), 2950 (s), 1500 (s), 1462 (s), 1390 (m), 1068 (m), 1035 (m), 912 (m), 745 (s), 700 cm^{-1} (s); nmr (CCl_4) δ 0.86 (d, 3 H, J = 6.0 Hz, CH_3), 1.11–2.00 (m, 5 H, $C^4H_2C^3H_2C^2H$), 2.52 (apparent q, 4 H, benzylic), and 7.10 ppm (s, 10 H, aromatic); mass spectrum (70 eV) m/e (rel intensity) 77 (5), 91 (100), 105 (15), 149 (9), 147 (30), 238 (22), 239 (5), 240 (0.7); mass, calcd. for $C_{18}H_{22}$, 238.1721 (found, 238.1728).

2-Phenylbenzosuberane (**6a**).—2-Benzosuberone[14] reacted with phenylmagnesium bromide to give 2-phenyl-2-benzosuberol: mp 82–83°; 60% yield; ir (Nujol) 3500 (s), 1495 (s), 1460 (s), 1390 (s), 1180 (m), 1100 (m), 1075 (s), 1015 (s), 778 (m), 725 (s), and 702 cm^{-1} (s); nmr (CCl_4) δ 1.66 [s, 1 H, OH (exchangeable with D when treated with D_2O)], 1.50–2.18 (m, 4 H, C^3H_2-C^4H_2), 2.74–2.98 (m, 2 H, C^5-benzylic), 2.88–3.60 (AB pattern, 2 H, J = 14 Hz, C^1H_2), 6.93–7.63 (m, 4 H, aromatic), and 7.10 ppm (s, 5 H, aromatic). 2-Phenyl-2-benzosuberol was subjected to catalytic hydrogenolysis as before[10a] and the product 2-phenylbenzosuberone (**6a**) was purified by preparative glpc (20 ft × 0.25 in. 30% SE-30 silicone gum rubber column operated at 255° with helium carrier gas at 60 psi) to give a viscous oil: n^{24}D 1.5844 (lit.[15] mp 37–38°); nmr (CCl_4) δ 1.30–2.33 (m, 4 H, $C^3H_2C^4H_2$), 2.42–3.43 [m (ABC pattern), 5 H, benzylic], 7.02 (s, 4 H, aromatic), and 7.16 ppm (s, 5 H, aromatic).

1-Benzyl-3,3-dimethylindan (**7b**) was synthesized by reaction of 3,3-dimethyl-1-indanone[3] with benzylmagnesium chloride followed by catalytic reduction of the intermediate carbinol so obtained by hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid:[10a] bp 180–190° (11 mm); $n^{26.8}$D 1.5672; nmr (CCl_4) δ 1.07 and 1.28 (both singlets, 6 H, gem methyls), 1.43–3.75 (unresolved, 5 H, all other nonaromatic), and 7.02–7.15 ppm (both singlets in a ratio of 5:4, 9 H, aromatic); mass, calcd for $C_{18}H_{20}$, 236.1565 (found, 236.1570).

1,1-Dimethyl-3-phenyltetralin (**8b**).—This was prepared by H_2SO_4-catalyzed cyclization of the previously obtained 2-methyl-4,5-diphenylpent-1-ene: bp 132–135° (0.27 mm); $n^{26.8}$D 1.5702; nmr (CCl_4) δ 1.30 and 1.13 (both singlets, 6 H, gem methyls), 1.84 (an apparent doublet, 2 H, C^2H_2), 2.70–3.38 [m with strong singlet at 2.90, 3 H, $CH_2CH(Ph)$], and 6.85–4.70 ppm (m with strong singlet at 7.18, 9 H, aromatic); mass, calcd for $C_{18}H_{20}$, 236.1565 (found, 236.1563).

Registry No.—**1a**, 31444-33-4; **1b**, 31444-34-5; **2b**, 31444-35-6; **3b**, 31444-36-7; **6a**, 2979-01-3; **7b**, 31489-88-0; **8b**, 31444-38-9; **10b**, 31444-39-0; 2-methyl-4,5-diphenylpentan-1-ol, 31489-89-1.

(12) G. Wittig, H. Eggers, and P. Duffner, *Justus Liebigs Ann. Chem.*, **619**, 20 (1958).

(13) K. L. Rinehart, Jr., and E. G. Perkins in "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 444.

(14) T. A. Crabb and K. Schofield, *J. Chem. Soc.*, 4276 (1958).

(15) H. Nozaki, M. Yamabe, and R. Noyori, *Tetrahedron*, **21**, 1657 (1965).

Cyclialkylation of Phenol with 1,5-Hexadiene

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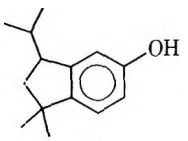
Received February 10, 1971

Phenol and 1,5-hexadiene (**6**) in carbon disulfide (4:1 mole ratio) at 30° react in the presence of boron trifluoride etherate to produce 5,6,7,8-tetrahydro-5,8-dimethyl-1- and -2-naphthol (**7** and **8**) and 2,5-diphenoxyhexane (**9**). A study of this reaction suggests that 5-phenoxy-1-hexene (**12**) and 2-(1-hexen-5-yl)phenol (**13**) are initially formed and react further to produce **9** and **7**, respectively. At longer reaction times, $C_{18}H_{26}O$ products are formed by reaction of **9** with **7** or $C_{12}H_{16}O$ ethers formed from **7**. Direct para alkylation by olefins **6** or **12** is excluded. The major para-alkylated product is formed from the alkylation of phenol with diether **9**.

The Lewis acid catalyzed reaction of phenol with cyclialkylating agents has been characterized by a diversity of products;[1,2] compounds **1–4** have been obtained starting with 2,5-dimethyl-1,5-hexadiene while **2** and **5** have been obtained from 2,5-dichloro-2,5-dimethylhexane.

1



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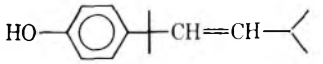

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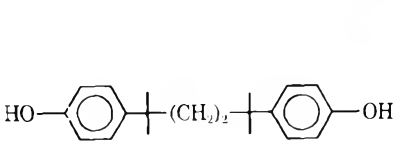

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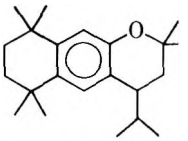
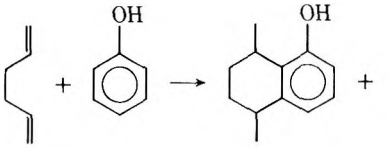
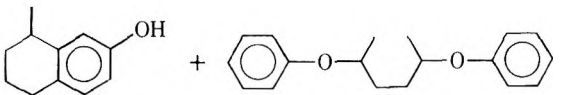


5

When phenol and 1,5-hexadiene (**6**) (4:1 mole ratio) at 30° reacted in the presence of boron trifluoride etherate for 3 hr, cycliadducts **7** and **8** were recovered in 27 and 8% yields, respectively, based on starting **6**. When the reaction was terminated after 15 min, **7** and diether **9** (25% yield) were the major products.[3] The



6 **7**



8 **9**

(1) H. A. Bruson and J. W. Kroeger, *J. Amer. Chem. Soc.*, **62**, 36 (1940).

(2) D. G. Jones and P. E. Schick, British Patent 706424 (1954); *Chem. Abstr.*, **49**, 9036*g* (1955).

(3) The identification of new compounds is based on ir and proton nmr spectra in addition to microanalyses: see the Experimental Section.

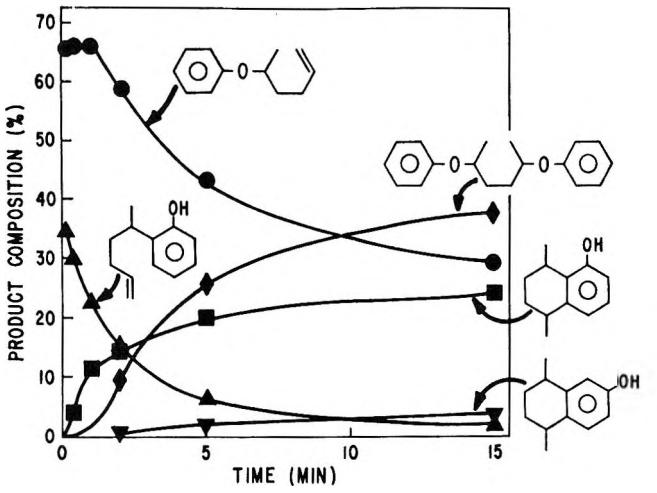


Figure 1.—Product composition from the reaction of phenol and 1,5-hexadiene (6): 0–15 min.

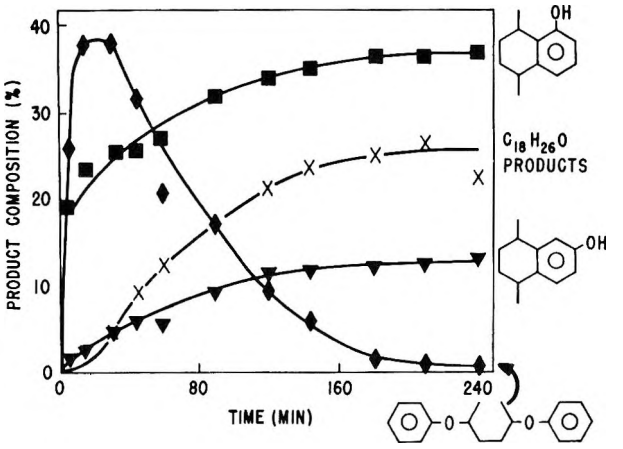
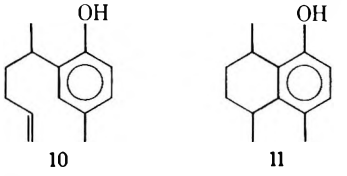


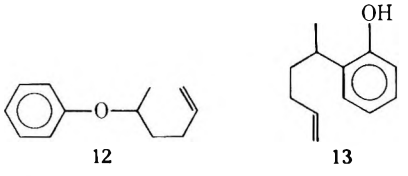
Figure 2.—Product composition from the reaction of phenol and 1,5-hexadiene (6): 0–240 min.

only previously reported cyclialkylation using **6** was performed on *p*-cresol, and led to the formation of **10** in addition to cycliadduct **11**.[4] In view of the com-



plexity of previous cyclialkylations and the fact that the *p*-cresol–**6** reaction is not comparable to the phenol–**6** reaction because of the blocked para position, we have studied the reaction of phenol with **6** in greater detail.

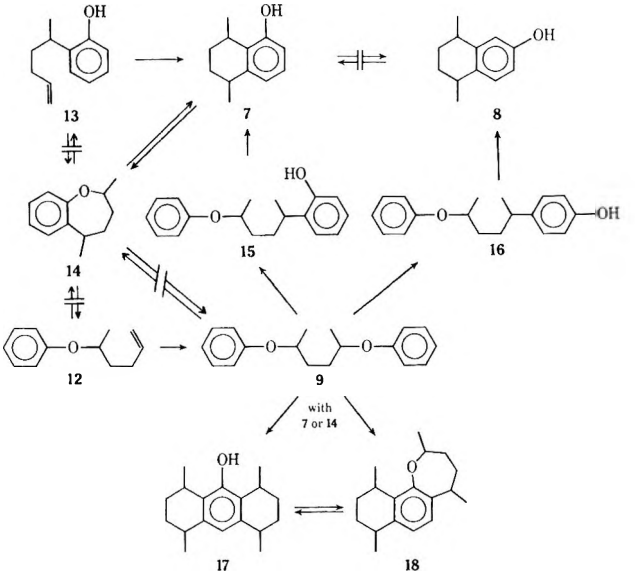
The initial step in elucidating the mechanism of the cyclialkylation was to determine the product distribution *vs.* time. When the reaction was followed by glpc, two substances, one compound **12**[3] and the other probably **13**, were shown to be the initial products formed in a ratio of 1.94 ± 0.20 while additional $C_{12}H_{16}O$ and $C_{18}H_{26}O$ compounds appear later in the reaction.



The identification of **13**, which is not present in sufficient quantities for isolation, is based on that fact that it is generated from phenol and **6**, it is the precursor of **7** but not **8** (*vide infra*), the glpc retention time is similar to that of **7** and 2-(2-hexyl)phenol, its formation is analogous to that of **10** from *p*-cresol and **6**,[4] and the fact that phenol and 1-hexene under similar conditions produce 2-phenoxyhexane and 2-(2-hexyl)phenol as the initial products[3] in a ratio of 1.56 ± 0.22 with no para-substituted or rearranged products observed.

A plot of product composition *vs.* time is shown in Figures 1 and 2 and, in more detail, in Table I in the Experimental Section. Scheme I depicts the reaction pathways observed in the study of the product composition *vs.* time and studies in which the individual reaction components are isolated and independently reacted with phenol and boron trifluoride etherate in carbon disulfide.

SCHEME I



It appears from an examination of Figure 1 that monoether–monoolefin **12** is the precursor of diether **9** and that the 2,3 cycliadduct **7** is formed from the compound tentatively assigned structure **13**. When **12** is isolated and treated with phenol and boron trifluoride etherate, **9** is the only observable product; small amounts of **7** (*ca.* 0.1% of the amount of **9** after 11% reaction) can be explained as being derived from phenol and **9** (*vide infra*). Therefore, **12** is not a direct precursor of **7**, and a route involving the intermediacy of **14** in a "walk-around" mechanism can be eliminated. By default, **13** is the sole intermediate in the formation of **7** which is observed in the early stages of the reaction.

A similar experiment performed on **7** reveals that it does not isomerize to **8**, but slowly equilibrates with at least four $C_{12}H_{16}O$ ethers (glpc retention times comparable to, but not identical with, that of **12**). While one likely structure is **14**, the structure of these ethers was not investigated further. The fact that 15% of **7** rearranges after 2.5 hr while 22% is isomerized after

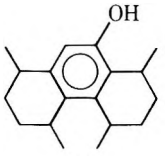
(4) E. A. Viktorova, E. A. Karakhanov, A. N. Shuikin, and N. I. Shuikin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 523 (1966); *Chem. Abstr.*, **65**, 8802a (1966).

20 hr indicates that the conversion to ethers is reversible and that the 7:14 equilibrium ratio under these conditions is *ca.* 3.5:1. Compound **8** was shown to be stable in the presence of phenol and boron trifluoride etherate over a period of 20 hr.

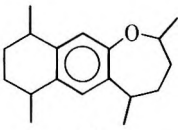
When diether **9** is treated with phenol and boron trifluoride etherate, two high-boiling transient products are observed in the ratio of 3.5:1. Subsequently, **7** and **8** are formed in a comparable ratio as the high-boiling compounds diminish. The fact that **7** and **8** are formed from **9** in what must reasonably be a two-step reaction, coupled with the preliminary appearance and subsequent disappearance of the high-boiling compounds, indicates that these transient products probably are intermediates in the conversion of **9** to **7** and **8**. Although isolation was not possible, reasonable tentative structures for these intermediates are **15** and **16**. It should be noted that diether **9** is the only source of the 3,4-cycliadduct **8** in the system.

Two $C_{18}H_{26}O$ products were also observed in this reaction. These compounds were identified as **17** and **18** based on spectral evidence[3] and evidence that (1) **17** equilibrates with **18** on treatment with boron trifluoride etherate in a manner similar to the equilibration of **7** and **14**, (2) **17** and **18** are formed from **7** and/or **14**, and (3) ortho alkylation predominates in this system.

The fact that **19** and **20** would exhibit ir and nmr spectra similar to those of **17** and **18**, coupled with the possibility that they could equilibrate, does not permit their exclusion as possible alternatives to **17** and **18**. It should be noted, however, that in related experiments we have detected steric retardation to 2,3-cyclialkylation when *p*-cresol is used in place of phenol,[5] and this would also argue for the formation of **17** instead of **19**.



19

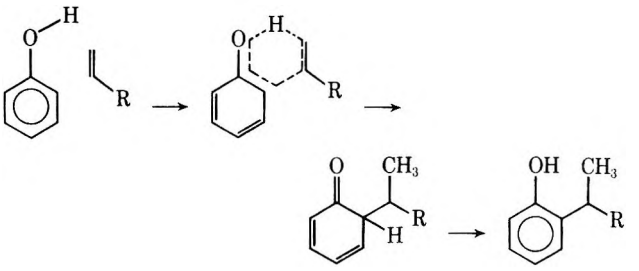


20

Data from the treatment of **9** with phenol and boron trifluoride etherate also indicates that the availability of **7** and/or **14** appears necessary for the formation of **17** and **18** because the (**7** + **14** + **15**):(**8** + **16**) ratio decreases with time as **17** and **18** are formed.

Although there is no need to invoke the alkylation of **8** in the formation of **17** and **18**, this experiment does not rule out the possibility of such a path, but indicates that the **9**–**7** and/or **14** reaction is the major secondary reaction leading to $C_{18}H_{26}O$ products.

The observation of exclusive ortho alkylation of the phenol ring by an olefin may appear unusual only because little work has been done on the kinetic alkylation which would separate direct alkylation by an olefin and secondary alkylation by an alkyl phenyl ether. Direct ortho alkylation by an olefin has been reported for thermal reactions[6] and reactions catalyzed by boron trifluoride[7] and aluminum phenolate.[8] The mechanism previously suggested[6,8] pictures the reaction proceeding through a six-center transition state assisted by Lewis acid coordination at oxygen and possibly at the double bond.



In conclusion, it has been shown that phenol and 1,5-hexadiene (**6**) react in the presence of boron trifluoride etherate to produce 5-phenoxy-1-hexene (**12**) and a transient intermediate tentatively identified as 2-(1-hexen-5-yl)phenol (**13**) which further react to give 2,5-diphenoxyhexane (**9**) and 5,6,7,8-tetrahydro-5,8-dimethyl-1-naphthol (**7**), respectively. Direct para alkylation by olefins **6** or **12** is excluded; the major para-alkylated product (**8**) is formed from the alkylation of phenol with diether **9**.

Experimental Section

Methods.—Proton nmr spectra were recorded on a Varian A-56/60 spectrometer and chemical shifts are reported in parts per million downfield from TMS. Infrared spectra were recorded on a Perkin-Elmer 21 spectrophotometer. Spectra and elemental analyses were obtained from the Analytical Laboratory of Corporate Chemical Research, Allied Chemical Corp.

All reagents were obtained from Baker and Adamson or Aldrich, and were used as received.

Unless specifically mentioned, no evidence was obtained to indicate the presence of more than one stereoisomer or diastereoisomer in any structure mentioned; on the other hand, the presence of more than one isomer, or isomer fractionation during work-ups, cannot be discounted.

Phenol and 6 (3 Hr).—A solution of 376 g (4.00 mol) of phenol, 82 g (1.00 mol) of **6**, and 20 ml of boron trifluoride etherate in 500 ml of carbon disulfide was stirred at 30° for 3 hr and then poured onto ice water. The organic phase was separated and dried (Na_2SO_4), and the products were fractionated by distillation through a 15-cm Vigreux column. In addition to recovered phenol, there was obtained 20 g, bp 45–70° (0.4 mm), 51 g, bp 70–100° (0.4 mm), and 29 g, bp 100–150° (0.4 mm).

Redistillation of the first fraction afforded 14 g (7% yield based on starting 1,5-hexadiene) of clear liquid, bp 56–62° (0.4 mm), identified as isomeric $C_{12}H_{16}O$ ethers (*e.g.*, **14**): nmr ($CDCl_3$) δ 0.8–1.9 (m, 10, CH_3 and CH_2, characterized by a pair of d centered at 1.23 and 1.27; J = 7.0 and 6.0 Hz, respectively, indicating the predominance of a seven-membered ring as in **14**), 2.40–3.08 (m, 1, ArCH), 3.35–4.15 (m, 1, ArOCH), and 6.65–7.20 ppm (m, 4, ArH); ir (neat) 750 (1,2-disubstituted aromatic) and 1238 cm^{-1} (Ar–O); no O–H was observed.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.84; H, 9.35.

Redistillation of the 70–100° (0.4 mm) fraction afforded 47.5 g (27% yield based on starting **6**) of clear liquid, bp 85–86° (0.4 mm), identified as 5,6,7,8-tetrahydro-5,8-dimethyl-1-naphthol (**7**): nmr (CCl_4) δ 1.2 (pair of d, 6, J = 7 Hz, CH_3), 1.3–2.2 (m, 4, CH_2), 2.6–3.3 (m, 2, ArCH), 5.16 (s, 1, OH), and 6.2–7.0 ppm (m, 3, ArH);[9] ir (neat) 740, 790 (1,2,3-trisubstituted aromatic), 1270 (Ar–O), and 3400 cm^{-1} (O–H).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.67; H, 8.91.

The 100–150° (0.4 mm) fraction was dissolved in 200 ml of

(5) J. M. Balquist, unpublished results.

(6) R. G. Anderson and S. H. Sharman, *Amer. Chem. Soc., Div. Petrol. Chem. Prepr.*, **15**, (2), E-27 (1970).

(7) F. J. Sowa, H. D. Hinton, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **54**, 3694 (1932).

(8) R. Stroh, R. Seydel, and W. Hahn, "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Foerst, Ed., Academic Press, New York, N. Y., 1963, p 337.

(9) Aromatic pattern similar to that of 5,6,7,8-tetrahydro-1-naphthol; Sadtler nmr spectrum 2694M.

TABLE I

PRODUCT COMPOSITION FROM PHENOL AND 1,5-HEXADIENE (6)

Time, min	Unreacted phenol, %	Product composition, %, excluding phenol							
		7	8	9	12	13	17 and 18	$C_{12}H_{16}O$ ethers	Higher boiling products
0.08	99.9	0.0	0.0	0.0	65.5	34.5	0.0	0.0	0.0
0.33	99.4	4.1	0.0	0.0	66.0	29.8	0.0	0.0	0.0
1	97.8	11.5	0.0	0.0	66.2	22.4	0.0	0.0	0.0
2	91.2	14.0	0.1	9.5	58.5	15.6	0.0	2.3	0.0
5	82.3	19.8	1.8	25.9	43.3	6.2	0.0	3.0	0.0
15	81.5	23.7	2.7	37.7	29.2	2.0	0.0	4.0	0.0
30	79.0	25.7	4.7	38.3	17.0	0.0	4.7	4.2	3.3
45	76.2	25.5	6.0	31.7	14.0	0.0	9.8	4.7	6.7
60	74.1	28.2	5.6	20.5	11.5	0.0	12.6	5.8	6.8
90	78.0	31.9	9.2	17.7	9.6	0.0	17.1	5.6	6.7
120	78.7	34.0	11.2	9.2	8.9	0.0	21.8	6.5	5.6
150	81.0	34.6	11.4	6.3	7.8	0.0	23.0	7.8	6.6
180	80.3	36.7	12.0	1.5	8.5	0.0	25.0	7.8	6.5
210	79.0	36.0	12.5	1.4	7.6	0.0	26.6	8.3	3.8
240	81.0	36.8	13.2	0.9	7.3	0.0	22.2	8.4	8.4
1260	79.0	39.6	13.2	0.0	4.3	0.0	26.1	6.5	8.4

ether and extracted with five 100-ml portions of 10% aqueous sodium hydroxide. The aqueous phase was acidified with hydrochloric acid and the acidic water layer was extracted with two 100-ml portions of ether. The ether solution was dried (Na_2SO_4) and distilled to give 15.8 g (8%) of clear liquid, bp 108–109° (0.4 mm) identified as 5,6,7,8-tetrahydro-5,8-dimethyl-2-naphthol (**8**): nmr (CCl_4) δ 1.2 (paired d, 6, J = 7 Hz, CH_3), 1.3–2.2 (m, 4, CH_2), 2.4–3.1 (m, 2, ArCH), 6.0 (s, 1, OH), and 6.4–7.1 ppm (m, 3, ArH);[10] ir (neat) 813 (1,2,4-trisubstituted aromatic), 1242 (Ar–O), and 3370 cm^{-1} (O–H).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 82.06; H, 9.21.

2,5-Diphenoxyhexane (9).—When the above reaction (0.25 scale) was terminated after 15 min and the organic phase extracted with five 500-ml portions of 10% aqueous sodium hydroxide, distillation of the dried (Na_2SO_4) organic phase afforded 13.2 g of yellow liquid, bp 140–150° (0.5 mm). Recrystallization of this liquid from methanol afforded 8.1 g (25%) of white crystals, mp 68–72°, identified as 2,5-diphenoxyhexane (**9**). Further purification afforded an analytical sample: mp 74–76°; nmr ($CDCl_3$) δ 1.3 (d, 6, J = 7 Hz, CH_3), 1.8 (m, 4, CH_2), 4.1–4.6 (m, 2, CH), and 6.7–7.5 ppm (m, 10, ArH); ir (KBr) 685, 750 (monosubstituted aromatic), and 1240 cm^{-1} (Ar–O); no O–H was observed.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.78; H, 8.34.

5-Phenoxy-1-hexene (12).—A solution of 32.5 g (0.35 mol) of phenol, 20.7 g (0.25 mol) of **6**, 6 ml of boron trifluoride etherate, and 40 ml of carbon disulfide was stirred at 30° for 5 min and poured onto ice water; the organic phase was separated and extracted with five 100-ml portions of 10% aqueous sodium hydroxide solution. The organic phase was dried (Na_2SO_4) and distilled to give 2.5 g (6%) of clear liquid, bp 55° (0.4 mm), identified as 5-phenoxy-1-hexene (**12**): nmr ($CDCl_3$) δ 1.2 (d, 3, J = 6 Hz, CH_3), 1.5–1.9 (m, 2, aliphatic CH_2), 1.9–2.4 (m, 2, allylic CH_2), 4.3 (hextet, 1, J = 6 Hz, OCH), 4.7–5.2 (m, 2, $CH{=}CH_2$), 5.4–6.2 (m, 1, $CH{=}CH_2$), and 6.6–7.4 ppm (m, 5, ArH); ir (neat) 690, 750 (monosubstituted aromatic), 1240 (Ar–O), and 910, 995, 1643, 3020, and 3070 cm^{-1} (vinyl).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.99; H, 9.32.

1,2,3,4,5,6,7,8-Octahydro-1,4,5,8-tetramethyl-9-anthranol (17) and $C_{18}H_{26}O$ Ethers.—A solution of 164 g (2.00 mol) of 1,5-hexadiene and 94 g (1.00 mol) of phenol in 350 ml of carbon disulfide was treated with 20 ml of boron trifluoride etherate and stirred at 25–30° for 6 hr. The solution was cooled, diluted with 500 ml of ether, and extracted with five 250-ml portions of 10% aqueous sodium hydroxide solution; the organic phase was separated, dried (Na_2SO_4), and distilled. The 56-g fraction, bp 100–160° (1.0 mm), was carefully redistilled to give 42 g of yellow liquid, bp 120–130° (0.1 mm).

The yellow liquid was dissolved in 200 ml of hexane and chromatographed on a 4.2 × 60 cm column of silica gel and eluted with 10% chloroform in hexane. The first 300-ml fraction was discarded; the next 1500 ml was concentrated to dryness and crystallized from 25 ml of hexane at −20° to afford 5.3 g (2.1%) of a yellow powder, mp 141–144° after filtration. Further recrystallization afforded an analytical sample, mp 144–145°, identified as 1,2,3,4,5,6,7,8-tetrahydro-1,4,5,8-tetramethyl-9-anthranol (**17**): nmr (CCl_4) δ 1.18 (d, 12, J = 7.0 Hz, $CHCH_3$), 1.30–2.18 (m, 8, CH_2), 2.55–3.14 (m, 4, ArCH), 4.44 (s, 1, OH), and 6.40 ppm (s, 1, ArH); ir (KBr) 868 (pentasubstituted aromatic), 1120–1235 (several absorptions which could be ascribed to Ar—O), and 3160 cm^{-1} (O–H).

Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.64; H, 10.25.

The mother liquor from the initial crystallization of **17** was concentrated and redistilled to give 6.2 g (3.0%) of a pale yellow liquid identified as an isomeric mixture of $C_{18}H_{26}O$ ethers: nmr ($CDCl_3$) δ 1.15–2.20 (m, 20, CH_2 and CH_3), 2.6–3.1 (m, 3, ArCH), 3.3–4.2 (m, 1, ArOCH), and 6.7–7.2 ppm (m, 2, ArH); ir (neat) 810 (1,2,3,4-tetrasubstituted aromatic) and 1200–1250 cm^{-1} (several absorptions which could be Ar–O); a medium band at 863 cm^{-1} might be due to 1,2,4,5-tetrasubstituted aromatic absorptions. The aliphatic nmr pattern and the glpc peak width indicate that this fraction probably is a mixture.

Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.60; H, 10.04.

Compound **17** is soluble in Claisen's alkali,[11] and extraction of a hexane solution of **17** and $C_{18}H_{26}O$ ethers represents another method of separating **17** from the ethers.

Phenol and 6. Product Composition *vs.* Time.—A solution of 31.6 g (0.336 mol) of phenol, 6.9 g (0.084 mol) of **6**, and 40 ml of carbon disulfide was heated to 30° by means of an oil bath, and 6 ml of boron trifluoride etherate was added; 2 ml aliquots were periodically removed, poured onto 20 ml of water, and shaken; and the organic phase was separated and analyzed by glpc on a 5 ft × 0.25 in. copper tube packed with 5% Triton X-100 on 45–50 mesh Chromosorb W inserted into an F & M Model 720 dual column gas chromatograph programmed at 8°/min starting at 60°. A type W weight-sensitive thermal conductivity detector was used, and therefore the reported percentages are weight per cent. Using a He flow of 60 cc/min, the following retention times (compound) were obtained: 5.5–8.0 ($C_{12}H_{16}O$ ethers), 6.5 (**12**), 9.2 (phenol), 18.6 (**13**), 20.3 (**7**), 22.2 (**8**), 24.3 (**9**), and 25.0–26.1 min (**17** and **18**).

The results are shown in Table I; peak areas are normalized to 100% after excluding phenol and carbon disulfide. In cases where there are traces of additional compounds, the products shown would not total 100%. For the purpose of this experiment

(10) Aromatic pattern similar to that of 3,4-dimethylphenol; Sadtler nmr spectrum 193M.

(11) For previous observations of the solubility of hindered ortho-disubstituted phenols in Claisen's alkali (*ca.* 35% aqueous methanolic potassium hydroxide, see ref 8, p 354. We thank a referee for suggesting this experiment.

all observable peaks with retention times longer than 26.1 min are listed as "higher boiling products."

Reactions at times shorter than 1 min were performed individually in a 25-ml beaker using 0.8 g of **6**, 3.0 g of phenol, and 5 ml of carbon disulfide. T_0 was taken as the time at which 1 ml of boron trifluoride etherate was added rapidly; the reaction was quenched when 10 ml of water was added rapidly. The reaction was then worked up as before.

Treatment of 7, 8, 9, 12, and 17 with Phenol and Boron Trifluoride Etherate.—A solution of 1.0 g of either **7**, **8**, **9**, **12**, or **17**, 5.0 g of phenol, and 15 ml of carbon disulfide was heated to 30°; 1 m of boron trifluoride etherate was added, and 2 ml aliquots were removed, quenched, and analyzed as before. The compounds tentatively identified as **15** and **16** were observed at 29.9 and 32.2 min, respectively, under the glpc conditions previously described. The percentages of the products from **7**–**9** and **12**, excluding phenol and carbon disulfide, are shown in Table II.

TABLE II

Compound **7**

Time, min	7	$C_{12}H_{16}O$ ethers[a]
150	84.8	15.2
1200	78.2	21.8

Compound **8**

Chromatographs recorded at 5, 15, 30, 90, 180, and 1200 min revealed **8** as the only compound excluding phenol

Compound **9**

Time, min	7	8	9	15
5	1.0	0.2	94.8	3.5
15	5.2	1.5	85.7	5.5
30	15.2	4.8	79.3	0.0
150	41.6	19.9	20.0	0.0

Time, min	16	17 and 18	$C_{12}H_{16}O$ ethers[b]
5	0.5	0.0	0.0
15	1.8	0.0	0.6
30	0.0	0.0	0.7
150	0.0	8.8	5.9

Compound **12**

Time, min	7	9	12
1	0.1	10.9	89.0
2	0.4	20.5	79.1
5	1.2	32.6	66.2

[a] A minimum of four peaks were observed; the peak corresponding to **12** was not observed. [b] Compound **12** is not present.

Compound 17.—Treatment of **17** leads to an equilibration of **17** with $C_{18}H_{26}O$ ethers in a reaction comparable to the equilibration of **7** with $C_{12}H_{16}O$ ethers. The appearance of a new ir absorption at 810 cm^{-1} indicates that the predominant substitution pattern of the ethers is 1,2,3,4 (as shown in **18**) although a band at 868 cm^{-1} could obscure the 1,2,4,5-tetrasubstitution pattern. The compounds could not be resolved by glpc.

Phenol and 1-Hexene.—A solution of 94 g (1.00 mol) of phenol, 28 g (0.33 mol) of 1-hexene, 6 ml of boron trifluoride etherate, and 100 ml of carbon disulfide was stirred at 30° for 30 min, and poured onto 200 ml of ice water; the organic phase was separated, washed with three 200-ml portions of 10% aqueous sodium hydroxide solution, and dried (Na_2SO_4). Distillation of the organic phase afforded 15 g of clear liquid, bp 71–73° (0.8 mm), 11.5 g, bp 74–92° (0.8 mm), and 3.6 g of clear liquid, bp 93–94° (0.8 mm).

The fraction with bp 71–73° (0.8 mm) is identified as 2-phenoxyhexane: nmr (neat) δ 0.7–1.1 (m, 3, CH_2CH_3), 1.1–1.8 (m, 9, aliphatic H with $OCHCH_3$ at 1.16, d, J = 6 Hz), 3.9–4.4 (sextet, 1, J = 6 Hz, OCH), and 6.6–7.3 ppm (m, 5, ArH); ir (neat) 692, 750 (monosubstituted aromatic), and 1235 cm^{-1} (Ar–O).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.92; H, 10.30.

The fraction with bp 93–94° (0.8 mm) is identified as 2-(2-hexyl)phenol: nmr (CCl_4) δ 0.7–1.0 (m, 3, CH_2CH_3), 1.0–1.8 (m, 9, aliphatic H with $ArCHCH_3$ at 1.27, d, J = 7 Hz), 2.8–3.3 (q, 1, J = 7 Hz, ArCH), 5.55 (broad s, 1, OH), and 6.7–7.2 ppm (m, 4, ArH); ir (neat) 750 (1,2-disubstituted aromatic), 1220 (Ar–O), and 3400 cm^{-1} (O–H).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.86; H, 10.28.

Phenol and 1-Hexene. Product Composition *vs.* Time.—A solution of 15.8 g (0.17 mol) of phenol, 3.4 g (0.04 mol) of 1-hexene, and 40 ml of carbon disulfide was heated to 30°; 3 ml of boron trifluoride etherate was added and 2-ml aliquots were periodically removed, quenched, and analyzed as before. 2-Phenoxyhexane and 2-(2-hexyl)phenol (retention times 6.2 and 15.4 min, respectively, under conditions previously described) were the only products observed over a period of 10 min.

Time, min	2-Phenoxyhexane, %	2-(2-Hexyl)phenol, %
1	57.0	43.0
2	60.5	39.5
10	65.4	34.6

Registry No.—**6**, 592-42-7; **7**, 31382-69-1; **8**, 31382-70-4; **9**, 31382-71-5; **12**, 31382-72-6; **13**, 31382-73-7; **14**, 31376-80-4; **17**, 31428-90-7; **18**, 31376-81-5; phenol, 108-95-2.

Acknowledgments.—We are indebted to Mr. Edward Manahan and Mr. John Frank of Allied Chemical Corporation for technical assistance.

Tricyclo[3.2.1.0^{3,6}]octan-7-yl Derivatives. Synthesis, Chemistry, and Solvolytic Studies[1]

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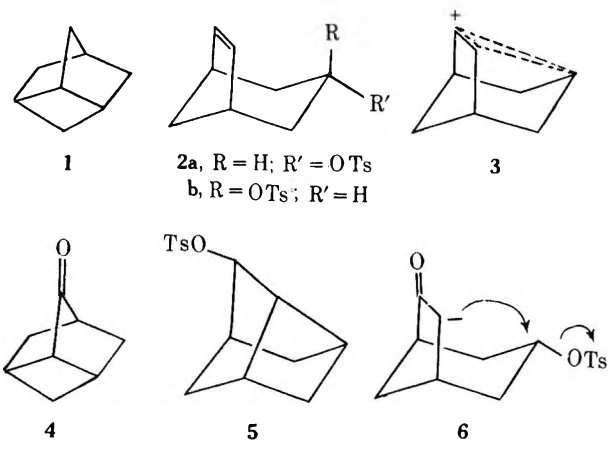
An intramolecular, base-catalyzed ring closure of *exo*-bicyclo[3.2.1]octan-6-on-3-yl tosylate (**6**) furnished the symmetrical ketone, tricyclo[3.2.1.0^{3,6}]octan-7-one (**4**), in good yield. The bicyclic precursor **6** was prepared from dehydronorcamphor by the sequence: dichlorocarbene addition and ring expansion, reductive removal of the two chlorine atoms, and introduction of the exo-C_3 oxygen atom by hydroboration–oxidation. The stereoselective and regioselective nature of the hydroboration reaction was established unambiguously. Wolff–Kishner reduction of ketone **4** gave the known parent hydrocarbon. Baeyer–Villiger oxidation of **4** gave a single lactone resulting from formal migration of the cyclobutane ring. Product distribution and deuterium label scrambling results suggest that solvolysis of tricyclo[3.2.1.0^{3,6}]octan-7-yl tosylate proceeds through a symmetrical, degenerate tricyclic cation to yield both tricyclic and bicyclic products.

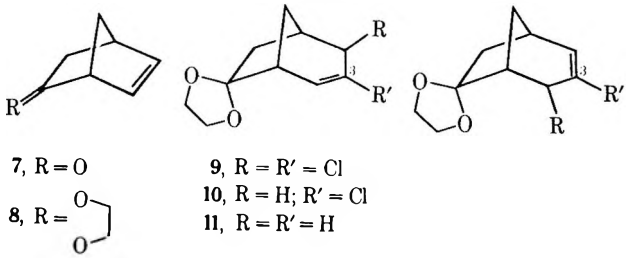
Concurrent interest in synthetic approaches to polycyclic skeletons common to naturally occurring systems and in the nature of cationic interconversions within the tricyclooctane–bicyclooctene carbon systems led to an examination of C_7-functionalized derivatives of tricyclo[3.2.1.0^{3,6}]octane (**1**). Considerable attention has been focused on the nature and scope of carbonium ion rearrangements in the various bicyclooctene systems.[2-5] In particular, the possibility of remote (homoallylic) double bond participation during solvolysis of *exo*- (and *endo*-) bicyclo[3.2.1]oct-6-en-3-yl tosylate (**2**) to give cation **3** as an intermediate has been examined.[6] No evidence for the postulated participation, however, was observed in these systems.[6] In contrast, ionization of C_7-substituted derivatives of **1** provides a direct route to the potentially degenerate tricyclic cation **3**. Herein we report the synthesis and some reactions of the symmetrical tricyclo[3.2.1.0^{3,6}]-octan-7-one (**4**) and the solvolytic behavior of the C_7 tosylate **5**.

Since the known synthetic entries[7-10] into the tricyclo[3.2.1.0^{3,6}]octane system are not suited for the preparation of C_7-functionalized derivatives, our initial synthetic efforts were directed toward the preparation of the key bicyclic intermediate, *exo*-bicyclo[3.2.1]-octan-6-on-3-yl tosylate (**6**). Formation of the tricyclic skeleton of **4** was then envisioned *via* a base-catalyzed intramolecular[11] ring closure (see arrows, **6**), a process requiring the exo-C_3 leaving group shown.[12]

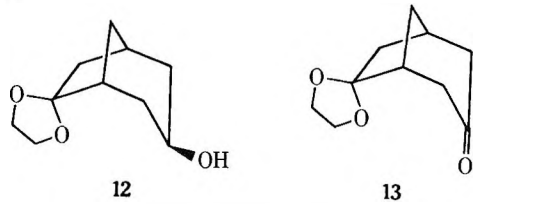
As a first step, the carbonyl group of dehydronorcamphor (**7**) was protected by acid-catalyzed conversion to the ethylene ketal **8**. The possibility of cationic skeletal rearrangements during ketal formation was excluded by reconversion to ketone **7**. Dichlorocarbene addition to ketal **8** followed by ring expansion[13] of the unstable dichlorocyclopropane adduct during distillation then yielded the isomeric dichlorides **9**. Sequential removal of the chlorine atoms by treatment with lithium aluminum hydride in tetrahydrofuran to give **10** and by lithium in liquid ammonia furnished the isomeric olefins **11**.



1 2a, R = H; R′ = OTs b, R = OTs; R′ = H 3 4 5 6



7, R = O 8, R = O O 9, R = R′ = Cl 10, R = H; R′ = Cl 11, R = R′ = H



12 13

Examination of the bicyclo[3.2.1] skeleton of **11** suggested that an addition reaction sensitive to steric environment would ensure both the regioselectivity and the stereoselectivity required for the conversion of **11** to the C_3 exo derivative **12**. Since the C_3 position

(1) Financial support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

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(12) A preliminary report of part of this work has appeared: S. A. Monti and S.-S. Yuan, *Tetrahedron Lett.*, 3627 (1969).

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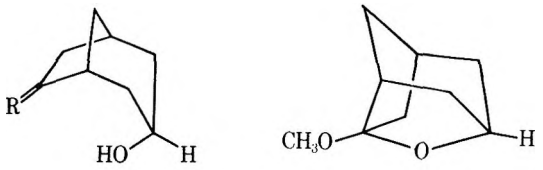
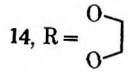
of **11** is the less hindered sp^2-hybridized carbon atom in both isomers and addition to the double bond should occur from the less hindered exo face,[14] both isomeric olefins **11** should yield the desired product **12**.

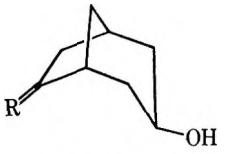
As anticipated, treatment of the olefin mixture **11** with disiamylborane,[15] followed by alkaline hydrogen peroxide oxidation, gave the C_3-exo ketal alcohol **12** in 84% yield. The skeletal position of the hydroxyl group was verified by careful oxidation[16] of **12** to give a *single* ketal ketone **13**. Exposure of **13** to deuterium oxide–potassium carbonate resulted in the incorporation of *four* deuterium atoms (mass spectrum). Thus the anticipated position selectivity was established since boron addition to C_2 or C_4 would lead ultimately to a ketal ketone (mixture) that would incorporate only two deuterium atoms. The exo orientation of the hydroxyl group in **12** was confirmed as follows. Lithium aluminum hydride reduction of ketal ketone **13** gave, as the major product, a new ketal alcohol **14**. The endo hydroxyl group assignment is based on the assumption that hydride addition will occur predominantly from the less hindered exo face.[14] This assignment was substantiated by conversion of the endo keto alcohol **15**, obtained from **14** by mild aqueous acid hydrolysis, to the cyclic ketal **16** upon treatment with anhydrous methanol,m agnesium sulfate, and a catalytic amount of *p*-toluenesulfonic acid.[17] The original exo ketal alcohol **12** was converted to keto alcohol **17** and then to the dimethyl ketal **18** when subjected to a similar reaction sequence.



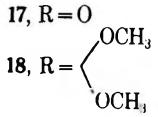
14, R = 

15, R = O

16

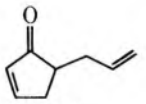


17, R = O

18, R = 

With the relative disposition of the functional groups now secure, the exo keto alcohol **17** was converted to tosylate **6**, the initial synthetic objective. The proposed intramolecular cyclization occurred smoothly upon treatment of a dilute benzene solution of **6** with potassium *tert*-butoxide to yield tricyclo[3.2.1.0^{3,6}]octan-7-one (**4**) in 62% yield. The spectral properties of this highly volatile solid were in complete accord with the proposed structure (see Experimental Section). Two additional products were also isolated from this reaction and they became the major products when cyclization was attempted in more concentrated solutions. Preliminary data indicate both possess at least a dimeric composition although structure elucidation is not complete. The two potential elimination products **19** (authentic samples were prepared from ketals **11**) were not formed during base treatment of tosylate **6** as judged by vpc analysis of the crude cyclization mixture. In addition, the absence of **20** or related monocyclic derivatives suggests that base-catalyzed fragmentation of **6** is not competitive with intramolecular cyclization.[18]

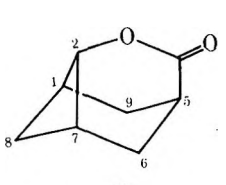
19



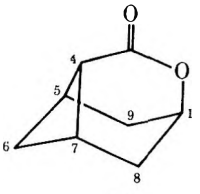
20

Wolff–Kishner reduction[6] of ketone **4** to the known parent hydrocarbon[7] **1** furnished final confirmation of the tricyclo[3.2.1.0^{3,6}]octane skeleton.

In connection with studies directed toward the total synthesis of cyclobutanoid terpenes, the Baeyer–Villiger oxidation of ketone **4** was examined. In theory, two lactones **21** and **22** are possible and both are derived by migration of a secondary alkyl group. Oxidation of **4** with buffered trifluoroperacetic acid yielded a single lactone in 98% yield. The general spectral properties of this material (see Experimental Section) were in accord with either formulation, **21** or **22**. An unambiguous structure assignment for the lactone was made using nmr spectroscopy.



21



22

Four distinct regions of absorptions were observed in the nmr spectrum of the lactone: δ 1.24 (1 H, doublet, J = 10 Hz), 2.0 (5 H, multiplet), 2.7 (3 H, multiplet), and 4.78 ppm (1 H, triplet, J = 5 Hz). The crucial difference between the two possible structures is that for **21**, the C_2 proton α to the oxygen atom (4.78 ppm) is coupled to the two equivalent bridgehead protons at C_1 and C_7 (2.7 ppm). For **22**, this proton (4.78 ppm) is coupled to *one* of the equivalent methylene proton pairs at C_8 and C_9 (2.0 ppm) (see respective figures for numbering). Spin decoupling at 2.7 ppm resulted in collapse of the 4.78-ppm signal to a sharp singlet; irradiation at 2.0 ppm did not affect the multiplicity of the 4.78-ppm signal but, as expected, did result in collapse of the 1.24-ppm doublet (exo proton at C_8) to a singlet. Thus, Baeyer–Villiger oxdation of the rigid ketone **4** results in preferential migration of the cyclobutyl group to yield lactone **21**.

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(15) D. J. Pasto and F. M. Flein, *J. Org. Chem.*, **33**, 1468 (1968); E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5281 (1968); S. P. Acharya and H. C. Brown, *J. Org. Chem.*, **35**, 196 (1970).

(16) R. H. Cornforth, J. W. Cornforth, and G. Popjak, *Tetrahedron*, **18**, 1351 (1962).

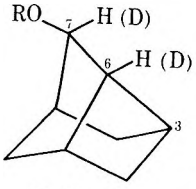
(17) The tricyclic ether skeleton of **16** is known: see ref 6 and P. Brun, M. Pally, and B. Waegall, *Tetrahedron Lett.*, 331 (1970).

(18) P. C. Mukharji and T. K. Das Gupta, *Tetrahedron*, **25**, 5275 (1969), and references cited therein.

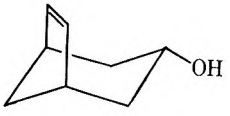
Reduction of the symmetrical ketone **4** with lithium aluminum hydride furnished the tricyclic alcohol **23** in good yield. The nmr spectra of the corresponding tosylate **5** and acetate **24** displayed clean, one-proton triplets (δ 4.50 ppm, J = 1.5 Hz, and 4.75 ppm, J = 1.5 Hz, respectively) for the proton on the hydroxyl-bearing carbon.

Solvolysis of tosylate **5** was examined in unbuffered acetic acid and in 80% acetone–water. Although decomposition accompanied solvolysis in acetic acid, no significant decomposition was observed in acetone–water. In order to facilitate analysis, the acetolysis products were saponified prior to analysis. The individual products were then identified by comparison of vpc retention times with those of authentic samples[19] and confirmed by peak enhancement experiments. Both the structures of the products and the composition of the mixtures were similar for the two solvent systems.

Three major products were obtained: tricyclic alcohol **23** and two bicyclic alcohols, *exo*-bicyclo[3.2.1]-oct-6-en-3-ol (**25**) and *exo*-bicyclo[3.2.1]oct-2-en-7-ol (**26**) in a ratio of *ca.* 10:10:1. Since decomposition accompanies solvolysis in acetic acid, the kinetic formation of other products cannot be excluded. During the very early stages of acetolysis, vpc analysis indicated the presence of small amounts of two additional products, **27** and **28**. These minor products disappeared rapidly and the composition ratio of major products remained essentially constant throughout the remainder of the acetolysis.[20] In acetone–water only the three major alcohol products were observed and their ratio remained constant with time.[21] Careful vpc analysis of the final product mixtures from both solvent systems showed that the endo alcohol **29** was not present.[22]



23, R = H
24, R = Ac
5, R = Ts



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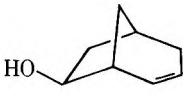
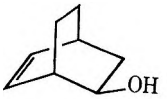
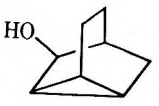


26



27



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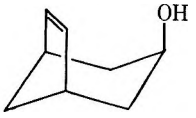
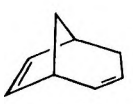


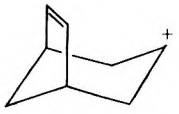
29

Acetolysis of the deuterium-labeled substrate **5** (C_7-*d*) was examined in order to ascertain the extent of rearrangement. The reappearance of a signal in the nmr spectrum corresponding to the proton on the hydroxyl-bearing carbon of, first, tosylate **5** (δ 4.50 ppm, doublet) and then tricyclic acetate **24** (δ 4.75 ppm, doublet) indicated that a scrambling process had occured.[23] The doublet multiplicity of the CHOR signal in both **5** and **24** confirmed that only a 1,2-C,C shift of the C_3–C_8 (or C_5–C_6) bond had occurred on ionization. Integration of the final reaction mixture indicated that the tricyclic acetate **24** was completely scrambled. Since the rate of internal return to give scrambled tosylate was greater than the rate of solvolysis, direct ionization of **5** to give scrambled acetate is not demanded. In separate control experiments it was established that **5** did not yield bicyclic tosylate **2** by internal return and that the C_7-labeled acetate **24** (C_7-*d*) was not scrambled under the solvolysis conditions.

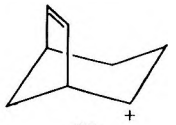
The symmetrically bridged species **3** or its equivalent of two rapidly equilibrating classical ion pairs appears to be the most economical intermediate to account for both the product distribution and the specific label scrambling results observed in the solvolysis of tosylate **5**. Solvent attack (or internal return) at the equivalent C_6 and C_7 sites in cation **3** clearly results in scrambled, tricyclic products, while attack at C_3, with inversion, accounts for the stereospecific formation of exobicyclic product **25**. As shown by LeBel[6] (for acetolysis), the minor bicyclic product **26** is not a primary solvolysis product but results from acid-catalyzed addition to bicyclo[3.2.1]octa-2,6-diene (**30**). Diene **30** is derived readily from **3** by deprotonation. The possible intermediary of the bicyclic cation **31** in product formation appears to be excluded by the observed product distribution. LeBel found[6] that solvolysis of both exo and endo bicyclic tosylates **2** occurred without double bond participation; exo tosylate **2a** yielded C_3 endo acetate (**29**, OH = OAc), and endo tosylate **2b** (possibly the more appropriate model for the case in hand) gave both exo and endo C_3 acetates (**25** and **29**, OH = OAc); and the major products from both epimers (64–73%) were derived from either a 1,2-hydride shift to give the C_2 cation **32** or deprotonation to give diene **30**. The absence of both the endobicyclic product **29** and significant hydride shift products (*e.g.*, **27** and **28**) appear to rule out the bicyclic cation **31** as an intermediate. An examination of molecular models provides a possible explanation for the difference in behavior between the tricyclic cation **3** and the bicyclic species **31**. In **31** the axial



30



31



32

hydrogens at C_2 are favorably disposed for hydride shift and/or elimination since their bond axes are parallel to the empty p orbital. The corresponding axial hydrogens in **3**, however, cannot achieve this optimum geometry for overlap due to the molecular distortions present in the tricyclic skeleton.

Kinetic examination of tosylate **5** in unbuffered acetic acid and in 80% acetone–water yielded approximate first-order constants of $k_{112°}$ (HOAc) = 8.4 × 10^{-6}

(19) We are most grateful to Professor N. A. LeBel for generously providing authenic samples; see ref 6.

(20) Isolated material balances in acetolysis were *ca.* 60–70%.

(21) Control experiments showed that acetate **24** and the acetate derived from alcohol **25** did not interconvert under solvolysis conditions although both did undergo some decomposition.

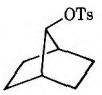
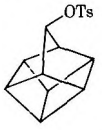
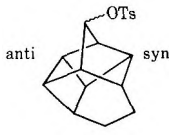
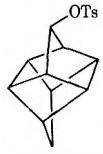
(22) Small amounts (*ca.* 5%) of unidentified, nonpolar materials were observed in both solvent systems.

(23) For analogous rearrangements in more complex polycyclic systems, see (a) P. v. R. Schleyer, J. J. Harper, G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *J. Amer. Chem. Soc.*, **89**, 698 (1967); (b) J. C. Barborak and R. Pettit, *ibid.*, **89**, 3080 (1967); (c) W. L. Dilling, R. A. Plepys, and R. D. Kroening, *ibid.*, **91**, 3404 (1969); (d) W. L. Dilling, C. E. Reineke, and R. A. Plepys, *J. Org. Chem.*, **34**, 2605 (1969).

sec^{-1} and $k_{113°}$ (acetone–H_2O) = 4.8 × 10^{-6} sec^{-1}. The rate of solvolysis of **5** is comparable to similar polycyclic systems and accelerated in comparison to simple 7-norbornyl tosylate (see Table I). Considera-

TABLE I

SOLVOLYSIS RATE CONSTANTS FOR SOME RELATED 7-NORBORNYL TOSYLATES (IN ACETIC ACID)

Compd	Rate	Ref
	$k_{110°}$ = 6.34 × 10^{-9} in 0.1 *M* potassium acetate	*a*
	$k_{125°}$ = 4.75 × 10^{-3}	23a
	Syn, $k_{120°}$ = 2.82 × 10^{-4} Anti, $k_{120°}$ = 5.07 × 10^{-5}	23c,d 23c,d
	$k_{120°}$ = 6.86 × 10^{-6}	*b*

[a] Extrapolated value from S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, **77**, 4183 (1955). [b] Quoted in ref 23d.

tion of the series of structurally related 7-norbornyl systems shown in Table I suggests that anchimeric assistance on ionization (relief of strain) is a significant contributor to the observed rate acceleration. In the absence of an unassisted reference model system (such as the 2-adamantyl system for unstrained secondary systems[24]), however, the relative contributions of nucleophilic solvent assistance (k_s) and anchimeric assistance (K_Δ) to the observed rate cannot be evaluated accurately.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B grating infrared spectrometer; nmr spectra were measured on a Varian Associates Model A-60 or HA-100 spectrometer. High-resolution mass spectra were obtained using CEC Model 21-100 mass spectrometer. The microanalytical determinations were done by the Chemalytics, Inc., Tempe, Ariz.

Bicyclo[2.2.1]hept-5-en-2-one Ketal (8).—A mixture of bicyclo[2.2.1]hept-5-en-2-one,[25] **7** (228.3 g, 2.11 mol), ethylene glycol (290 g), and *p*-toluenesulfonic acid (1 g) in benzene (750 ml) was refluxed for 20 hr with continuous separation of water (42 ml, 2.3 mol). Upon cooling, sodium bicarbonate (10 g) was added, and the glycol layer was separated and then extracted with ether (400 ml). After drying ($MgSO_4$) and evaporation of the solvent, the residue was distilled to give pure ketal **8**: 286.3 g (89%); bp 95–100° (30 mm); ir (film) 1200–1000 cm^{-1} (COC); nmr (CCl_4) δ 1.1–1.2 (m, 4, CH_2), 2.5–2.9 (m, 2, bridgehead), 3.8 (m, 4, OCH_2CH_2O), 6.0 (dd, 1, *J* = 5.5 and 3.5 Hz, C_5), and 6.25 ppm (dd, 1, *J* = 5.5 and 3 Hz, C_6); mol wt, calcd for $C_9H_{12}O_2$, 152.0837 (found *m/e*, 152.0840).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.04; H, 7.97.

2,3- (and 3,4-) Dichlorobicyclo[3.2.1]oct-3- (and -2-) en-6-one Ketal (9).—Under a nitrogen atmosphere, ethyl trichloroacetate (546 g, 2.86 mol) was added over a 6-hr period to an ice-cold mixture of ketal **8** (86.8 g, 0.57 mol) and sodium methoxide (200 g, 3.7 mol) in pentane (500 ml). After stirring for an additional 6 hr at 0° and 12 hr at room temperature, the mixture was diluted with water (200 ml) and extracted with pentane. The combined organic extracts were dried ($MgSO_4$) and concentrated. Distillation of the residue yielded pure product **9**: 104.4 g (77%); bp 120–130° (0.6 mm); ir (film) 1635, 1200–1000 cm^{-1}; nmr (CCl_4) δ 1.5–2.8 (m, 6), 3.89 (m, 4), 4.23 (d, 0.33, *J* = 2.5 Hz, CHCl), 4.50 (d, 0.67, *J* = 2.5 Hz, CHCl), 6.0 (dd, 0.33, *J* = 8.5 and 1 Hz), and 6.18 ppm (dd, 0.67, *J* = 8 and 1 Hz); mol wt, calcd for $C_{10}H_{12}O_2Cl_2$, 234.0214 (found *m/e*, 234.0222). The compound decomposed in air; microanalytical data were not reproducible.

3-Chlorobicyclo[3.2.1]oct-2- (and -3-) en-6-one Ketal (10).—Lithium aluminum hydride (3.9 g, 0.102 mol) was stirred in refluxing tetrahydrofuran (200 ml) under nitrogen. The dichloride **9** (7.5 g, 0.032 mol) was dropped into the suspension and heated for 1.5 hr. With ice cooling, water (7.5 ml) was added slowly to the reaction mixture and the resultant slurry was filtered through Celite. The solid collected on the funnel was washed with tetrahydrofuran and the combined solution was dried ($MgSO_4$) and evaporated. Distillation of the residue gave 5.3 g of product **10** (83%): bp 72–76° (0.06 mm); ir (film) 1648, 1120–1000 cm^{-1}; nmr (CCl_4) δ 1.5–3.0 (m, 8), 3.8 (m, 4), and 5.7–6.1 ppm (m, 1); mol wt, calcd for $C_{10}H_{13}O_2Cl$, 200.0604 (found *m/e*, 200.0615).

Anal. Calcd for $C_{10}H_{13}O_2Cl$: C, 59.86; H, 6.53. Found: C, 59.97; H, 6.57.

Bicyclo[3.2.1]oct-2- (and -3-) en-6-one Ketal (11).—A solution of vinyl chloride **10** (12 g, 0.06 mol) in 5 ml of ether was added dropwise to a solution of lithium (1.2 g, 0.2 mol) in liquid ammonia (200 ml) and then stirred for 1 hr. Ammonium chloride (15 g) was added and the ammonia was evaporated. Water (70 ml) was added and the mixture was extracted with ether. The ether solution was dried ($MgSO_4$) and concentrated. The residue was distilled to give 7.2 g of **11** (71%): bp 122–127° (30 mm); ir (film) 1100–1000 cm^{-1}; nmr (CCl_4) δ 1.4–2.6 (m, 8), 3.8 (m, 4), and 5.2–6.1 ppm (m, 2); mol wt, calcd for $C_{10}H_{14}O_2$, 166.0994 (found *m/e*, 166.0998).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.00; H, 8.60.

***exo*-Bicyclo[3.2.1]octan-3-ol-6-one Ketal (12).**—A solution of diborane in tetrahydrofuran (0.1 *M* solution, 145 ml) was injected *via* a hypodermic syringe into a stirred solution of 2-methyl-2-butene (28 g, 0.4 mol) in tetrahydrofuran (300 ml) at 0° under a nitrogen atmosphere. This mixture was stirred for 2 hr. The ketal **11** (30.8 g, 0.18 mol) was then added at 0° and the mixture was stirred at room temperature for 3.5 hr. The solution was heated to 50°, a solution of sodium hydroxide (6 *N*, 100 ml) was added, and then a solution of hydrogen peroxide (30%, 130 ml) was added. The resulting mixture was stirred at 50° for 2 hr. The aqueous layer was separated and extracted with ether (200 ml). After drying ($MgSO_4$) and evaporation, the residue was distilled to give 26.8 g (77%) of pure alcohol **12**: bp 90–95° (0.04 mm); ir (film) 3400, 1100–1000 cm^{-1}; nmr (CCl_4) δ 1.0–2.4 (m, 10) and 3.6–4.3 ppm (m, 6); mol wt, calcd for $C_{10}H_{16}O_3$, 184.1099 (found *m/e*, 184.1109).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.69; H, 8.79.

Bicyclo[3.2.1]octane-3,6-dione 6-Ketal (13).—Chromium trioxide (2 g, 20 mmol) was dissolved in 2 ml of water and added to pyridine[16] (20 ml). The alcohol **12** (1.1 g, 5.95 mmol) in pyridine (10 ml) was added and this mixture was stirred at room temperature for 3 days. The solution was quenched with water (50 ml), filtered through Celite, and extracted with ether. After drying ($MgSO_4$) and evaporation, the residue was chromatographed on a silica gel column (hexane–ether 3:1, v/v) to give 1.0 g (90%) of crystalline ketone **13**: mp 58–60°; ir (CCl_4) 1718 (C=O), 1120–1000 cm^{-1}; nmr (CCl_4) δ 1.6–2.7 (m, 10) and 3.7–4.1 ppm (m, 4); mol wt, calcd for $C_{10}H_{14}O_3$, 182.0943 (found *m/e*, 182.0941).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.58; H, 7.47.

Deuterium Incorporation of Bicyclo[3.2.1]octane-3,6-dione 6-Ketal (13).—A mixture of ketone–ketal **13** (59 mg, 0.32 mmol) and potassium carbonate (51 mg) in ether (3 drops) and deuterium oxide (0.5 ml) was stirred for 90 hr. The organic ma-

(24) J. M. Harris, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 5729 (1970), and references cited therein.

(25) P. K. Freeman, D. M. Balls, and D. J. Brown, *J. Org. Chem.*, **33**, 2211 (1968).

terial was extracted with carbon tetrachloride and evaporated to give 50 mg (85%) of deuterated **13**: nmr (CCl_4) diminished peaks δ 2.15, 2.25, 2.45, and 2.60 ppm (integration indicated a loss of 3.3 hydrogens); ir (CCl_4) 2200, 2130 cm^{-1}; mass spectrum *m/e* (rel intensity) 183 (2), 184 (5), 185 (10), 186 (7.5), and 187 (2); mol wt of **11**-d_0, 182.

endo-**Bicyclo[3.2.1]octan-6-on-3-ol Ketal** (**14**).—To a boiling suspension of lithium aluminum hydride (140 mg, 3.69 mmol) in tetrahydrofuran (20 ml) under nitrogen was added the ketone–ketal **13** (672 mg, 3.69 mmol) in 5 ml of tetrahydrofuran. The reflux was maintained for 8 hr and then 5 drops of water were added. The resultant slurry was filtered through Celite and the collected solid was washed with tetrahydrofuran. The combined organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column (ether–chloroform 1:1, v/v). The first fractions gave the liquid endo alcohol **14**, 500 mg (74%); the latter fractions yielded the exo alcohol **12**, 140 mg (20%). Pure[26] endo **14** showed ir (CCl_4) 3510, 1200–1000 cm^{-1}; nmr ($CDCl_3$) δ 1.2–2.5 (m, 10) and 3.7–4.1 ppm (m, 6).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.56; H, 8.66.

endo-**Bicyclo[3.2.1]octan-3-ol-6-one** (**15**).—A solution of ketal **14** (94 mg, 0.51 mmol), one crystal of *p*-toluenesulfonic acid monohydrate, and 1 ml of water in tetrahydrofuran (20 ml) was heated at reflux for 3.5 hr. The solution was cooled and washed with saturated potassium carbonate solution. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica gel, ether–hexane 1:1, v/v) to give 72 mg of glassy product[26] **15** (100%): ir (CCl_4) 3590, 3410, 1740, 1080 cm^{-1}; nmr (CCl_4) δ 1.7–2.7 (m, 10), 2.9 (s, 1), and 4.1 ppm (m, 1, CHOH); mass spectrum *m/e* (rel intensity) 140 (80, molecular ion), 122 (78), 81 (90), and 79 (100).

3-Methoxy-2-oxatricyclo[3.2.1.1^{3,7}]nonane (**16**).—A mixture of ketone–alcohol **15** (151 mg, 1.08 mmol), one crystal of *p*-toluenesulfonic acid monohydrate, and anhydrous magnesium sulfate (0.1 g) in methanol (25 ml) was heated at reflux for 6 hr. Then potassium carbonate (0.2 g) was added and the solution was filtered. The solvent was removed to give 120 mg of liquid product[26] **16** (71%): ir (CCl_4) 2930, 1325, 1080 cm^{-1}; nmr (CCl_4) δ 1.2–2.5 (m, 10), 3.3 (s, 3), and 4.4 ppm (m, 1); mol wt, calcd for $C_9H_{14}O_2$, 154.0994 (found *m/e*, 154.0994).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.59; H, 9.09.

exo-**Bicyclo[3.2.1]octan-3-ol-6-one** (**17**).—A mixture of ketal–alcohol **12** (2.1 g, 11 mmol), one crystal of *p*-toluenesulfonic acid monohydrate, and 0.2 ml of water in tetrahydrofuran (100 ml) was heated at reflux for 12 hr. After drying ($NaHCO_3$–$MgSO_4$) and evaporation, the residue was chromatographed on a silica gel column (ether) to give 1.3 g (81%) of pure ketone–alcohol **17**: mp 150–151°; ir ($CHCl_3$) 3400, 1740, 1040 cm^{-1}; nmr ($CDCl_3$) δ 1.2–2.8 (m, 10), 2.9 (s, 1, OH), and 3.6–4.2 ppm (m, 1, CHOH); mol wt, calcd for $C_8H_{12}O_2$, 140.0837 (found *m/e*, 140.0842).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.27; H, 8.79.

exo-**6,6-Dimethoxybicyclo[3.2.1]octan-3-ol** (**18**).—A mixture of ketone–alcohol **17** (171 mg, 1.2 mmol), one crystal of *p*-toluenesulfonic acid, and 0.2 g of anhydrous magnesium sulfate in 10 ml of methanol was heated at reflux for 18 hr. Then potassium carbonate (0.1 g) was added and the solution was filtered and concentrated. The residue was chromatographed on a silica gel column (hexane, then ether) to give 110 mg of liquid product[26] **18** (50%): ir ($CHCl_3$) 3580, 3400, 1100–1000 cm^{-1}; nmr ($CDCl_3$) δ 1.1–2.7 (m, 11), 3.15 (s, 3, OCH_3), 3.25 (s, 3, OCH_3), and 3.7–4.3 ppm (m, 1, CHOH); mass spectrum *m/e* (rel intensity) 186 (22, molecular ion), 169 (60), 168 (25), 155 (20), and 122 (100).

exo-**Bicyclo[3.2.1]octan-6-on-3-yl Tosylate** (**6**).—A solution of alcohol–ketone **17** (1.2 g, 8.6 mmol) and *p*-toluenesulfonyl chloride (2.2 g, 11.5 mmol) in 10 ml of dry pyridine was stirred at 0° for 3 hr. Then 100 g of ice was added. The crude product was filtered and was recrystallized from ether–benzene to give 2.4 g (90%) of product **6**: mp 81–82.5°; ir $CHCl_3$) 1740, 1600, 1190, 1160 cm^{-1}; nmr ($CDCl_3$) δ 1.5–2.8 (m, 3-CH_3 at 2.45), 4.2–4.8 (m, 1), 7.3 (d, 2, J = 8 Hz), and 7.8 ppm (d, 2, J = 8 Hz); mol wt, calcd for $C_{15}H_{18}SO_4$, 294.0926 (found *m/e*, 294.0932).

Anal. Calcd for $C_{15}H_{18}SO_4$: C, 61.20; H, 6.16; S, 10.87. Found: C, 61.48; H, 6.36; S, 10.70.

Tricyclo[3.2.1.0^{3,6}]octan-7-one (**4**).—The tosylate **6** (2.4 g, 8.15 mmol) in benzene (20 ml) was dropped into a stirred slurry of potassium *tert*-butoxide (1.5 g, 13.2 mmol) in benzene (30 ml) under nitrogen. After 3 hr, water (30 ml) was added and the two layers were separated. The aqueous solution was extracted with ether. The combined organic phases were dried ($MgSO_4$) and the solvent was removed by careful distillation. The oily residue was purified by "sublimation" (70°, 60 mm) to yield crystalline **4**: 611 mg (62%); mp 99–100.5° (sealed capillary); ir (CCl_4) 2930, 2860, 1763, 1150 cm^{-1}; nmr (CCl_4) δ 1.5–2.7 ppm (complex); mol wt, calcd for $C_8H_{10}O$, 122.0732 (found *m/e*, 122.0739).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.46; H, 8.04.

The 2,4-dinitrophenylhydrazone had mp 175–177°.

Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.46; H, 4.76; N, 18.50.

The residue remaining after sublimation (232 mg) was chromatographed on a silica gel column ($CHCl_3$) to give two substances: A (50 mg) [mp 197–200°; ir ($CHCl_3$) 2950, 1270, 1100–1000 cm^{-1}] and B (110 mg) [mp 138–140°; ir ($CHCl_3$) 3560, 2940, 2860, 1745, 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.3–2.8 ppm (complex); mass spectrum *m/e* 244 (molecular ion)].

Bicyclo[3.2.1]oct-2- (and -3-) en-6-one (**19**).—The olefin–ketal **11** (3.5 g, 21 mmol) was dissolved in acetone (30 ml) containing 3 ml of 10% hydrochloric acid and was stirred at room temperature for 6 hrs. This solution was neutralized with sodium bicarbonate and extracted. The concentrated liquid was chromatographed on a silica gel column (ether–hexane 1:8, v/v) to give 2.0 g of pure liquid **19** (77%): ir (CCl_4) 1730, 1630 cm^{-1}; nmr (CCl_4) δ 1.7–2.9 (m, 8) and 5.3–6.2 ppm (m, 2); mass spectrum *m/e* (rel intensity) 122 (50), 80 (34), 79 (100), 78 (93), and 77 (21).

Anal. Calcd for $C_9H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.86; H, 8.39.

Tricyclo[3.2.1.0^{3,6}]octane (**1**).—A mixture of ketone **4** (334 mg, 27 mmol), ethylene glycol (10 ml), and hydrazine hydrate (1.4 g, 274 mmol) was heated to 140°. Sodium methoxide (296 mg, 54.8 mmol) in 1 ml of methanol was added and the mixture was heated to 180° over a 3-hr period. Water (30 ml) was added, and the aqueous layer was separated and extracted with *n*-pentane. The pentane solution was dried ($MgSO_4$) and the solvent was distilled. The residue from distillation (100 mg) was sublimed at 50° (100 mm) to give 31 mg of pure hydrocarbon **1** (11%): mp 118–119° (sealed capillary) (lit.[7] mp 111–112°); ir (CCl_4) 2930, 2850, 1450, 1330, 1270, 1090 cm^{-1}; nmr (CCl_4) δ 1.3 and 1.6 (m, 6), 2.2, 2.45, and 2.85 ppm (m, 6); mass spectrum *m/e* (rel intensity) 108 (9), 79 (45), 67 (43), 66 (100). These data are in agreement with the literature.[7]

3-Oxatricyclo[3.3.1.0^{2,7}]nonan-4-one (**22**).[27]—Trifluoroacetic anhydride (1.02 g, 7 mmol) was added slowly to a vigorously stirred suspension of 90% hydrogen peroxide (Shell Chemical Co.) (0.16 g, 6 mmol) in methylene chloride (10 ml) at 0° and then stirred for 30 min. The peracid solution was then added slowly to a stirred mixture of disodium acid phosphate (1.6 g) and ketone **4** (511 mg, 4.9 mmol) in methylene chloride (10 ml) at 0°. The reaction mixture was stirred at room temperature for 6 hr and then it was filtered. The filtrate was washed with 10% sodium carbonate solution, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$) to give 670 mg of lactone **22** (98%): mp 136–138°; this material was homogeneous on tlc (silica gel) and on two vpc columns (SE-30 and FFAP); ir (CCl_4) 1770, 1150–1000 cm^{-1}; nmr (CCl_4), see text; mol wt, calcd for $C_8H_{10}O_2$, 138.0681 (found *m/e*, 1.38.0682).

Tricyclo[3.2.1.0^{3,6}]octan-7-ol (**23**).—A solution of ketone **4** (569 mg, 4.6 mmol) in ether (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (175 mg, 4.6 mol) in ether (5 ml) under nitrogen. After the mixture was heated for 4 hr, dilute hydrochloric acid (10%) was added carefully to dissolve all the solid present. The aqueous layer was separated and extracted with ether. The ethereal solutions

(26) This compound was judged homogeneous by silica gel tlc in chloroform and hexane–ether. Since a satisfactory combustion analysis was not obtained, the physical constants should be interpreted accordingly.

(27) This procedure is that previously described by E. E. Smissman, J. F. Muren, and N. A. Dahle, *J. Org. Chem.*, **29**, 3517 (1964).

were combined and dried ($MgSO_4$). The residue, after concentration, was sublimed at 70° (60 mm) to give 526 mg of waxy crystalline **23** (91%): mp 158–159°; ir (CCl_4) 3650, 3320, 2950, 1090, 1050 cm^{-1}; nmr (CCl_4) δ 1.1–2.7 (m, 10), 2.9 (s, 1), and 3.95 ppm (m, 1); mol wt, calcd for $C_8H_{12}O$, 124.0888 (found *m/e*, 124.0888).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 76.93; H, 9.85.

7-Deuteriotricyclo[3.2.1.0^{3,6}]octan-7-ol (**23**, C_7-*d*) was prepared as described above using lithium aluminum deuteride: ir ($CHCl_3$) 3600, 3400, 2940, 2140, 1130, 1060 cm^{-1}; nmr ($CDCl_3$) δ 1.1–2.7 (m, 10) and 1.8 (s, 1); mass spectrum *m/e* 125 (molecular ion).

Tricyclo[3.2.1.0^{3,6}]octan-7-yl *p*-Toluenesulfonate (5).—A solution of **23** (184 mg, 1.5 mmol) and *p*-toluenesulfonyl chloride (563 mg, 2.9 mmol) in 5 ml of dry pyridine was stirred at 0° for 2 hr. The solution was then stored at −5° for 12 hr until precipitation of pyridine hydrochloride was complete. The mixture was poured into ice–water (20 ml) and was extracted with ether. The ethereal solution was washed with dilute hydrochloric acid and then dried ($MgSO_4$) and concentrated. Column chromatography (silica gel) with ether–pentane (1:6, v/v) gave 323 mg of **5** (88%): mp 30–32°; ir ($CHCl_3$) 3020, 2950, 1600, 1370, 1180, 1160, 1100 cm^{-1}; nmr ($CHCl_3$) δ 1.2–2.8 (m, 10), 2.4 (s, 3, Ar CH_3), 4.5 (t, 1, J = 1.5 Hz), 7.3, and 7.7 ppm (two d's, 4, J = 8 Hz, aromatic H's); mass spectrum *m/e* 278 (molecular ion).

Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.73; H, 6.52; S, 11.50. Found: C, 64.88; H, 6.43; S, 11.55.

7-Deuteriotricyclo[3.2.1.0^{3,6}]octan-7-yl *p*-toluenesulfonate (**5**, C_7-*d*) was prepared from **23** (C_7-*d*) as described above: ir ($CHCl_3$) 3010, 2940, 2200, 1600, 1370, 1180, 1160 cm^{-1}; nmr ($CDCl_3$) δ 4.5 ppm (signal absent).

Solvolysis of Tricyclo[3.2.1.0^{3,6}]octan-7-yl *p*-Toluenesulfonate (5). Acetic Acid.—Combustion tubes containing tosylate **5** (53 mg, 0.19 mmol) and reagent grade glacial acetic acid with 1% added acetic anhydride (5 ml, 0.03 *M*) were purged with nitrogen, sealed, and then placed in a constant temperature bath at 112 ± 0.5°. After approximately 3–4 hr, the solutions turned dark blue-black and solid gradually appeared; after 10 half-lives a brown precipitate was present. Similar decomposition was observed in buffered (NaOAc) runs and the product composition was the same as in the unbuffered runs (*vide infra*). Tubes were removed after *ca.* 20, 40, 50, 70, and 80% reaction and opened, and the contents were diluted with water (25 ml). The aqueous solution was extracted with ether and, after concentration, the organic phase was saponified with potassium hydroxide in methanol. The resulting products were isolated by continuous pentane extraction of the methanol solution and characterized as described below.

Acetone–Water.—In a similar fashion, combustion tubes containing tosylate **5** and 80% acetone–water (*ca.* 5 ml, 0.03 *M*) were sealed under nitrogen and placed in a constant temperature bath at 113 ± 0.2°. No visual decomposition was observed over a period of *ca.* 10 half-lives. Tubes were removed after *ca.* 15, 30, 50, 80, and 95% reaction and opened, and the products were analyzed directly.

The products from both runs were identified by comparison of vpc retention times with authentic samples[19] using a 25% Dow Polyglycol E20,000 and 60–80 mesh Chromosorb W, 1/8 in. × 3 m column at 130°. In each case, product identity (or absence) was verified by peak enhancement experiments. In order of increasing retention times, the elution of the various products and authentic samples was **30** (1.5 min), **29** (19 min), **25** (31 min), **27** (33 min), **23** (34 min), **26** (36 min), and **28** (38 min). The observed product distributions are described in the text. In both solvent systems *ca.* 5% unknown, nonpolar (short retention time) products were observed.

Deuterium Scrambling.—A sample of C_7-deuterated tosylate **5** (59 mg) in acetic acid (0.4 ml) was heated in a sealed nmr tube at 120°. After 2 hr, nmr analysis of the now blue-black solution showed appearance of a doublet (J = 2 Hz) at δ 4.5 ppm corresponding to the C_7 hydrogen of tosylate **5**. This signal reached maximum intensity at 6 hr and then decreased gradually. A new doublet at 4.75 ppm (J = 2 Hz) corresponding to the C_7 hydrogen of acetate **25** appeared after *ca.* 4 hr and reached constant intensity after *ca.* 10 hr. Using the aromatic protons of the tosylate (and liberated *p*-toluenesulfonic acid) as an internal standard, integration showed that the tosylate **5** was completely scrambled after 6 hr and the product acetate **25** was completely scrambled.

Control Experiments. A.—A sample of C_7-deuterated tricyclic acetate **24**, prepared from C_7-deuterated alcohol **23** with acetic anhydride–pyridine, in acetic acid containing 1 equiv of *p*-toluenesulfonic acid was heated at 120° in a sealed nmr tube. No deuterium scrambling was observed by nmr after 15 hr. Vpc analysis of the resulting product showed only recovered starting material.

B.—The acetic acid solvolysis of tricyclic tosylate **5** was stopped after *ca.* 50% reaction and the unreacted tosylate was isolated by column chromatography. This material was identical with starting tosylate **5** as judged by the ir and nmr.

C.—Treatment of the acetate derived from alcohol[19] **25** with acetic acid containing 1 equiv of *p*-toluenesulfonic acid at 120° led to decomposition, but no tricyclic acetate **24** was formed as judged by vpc.

Kinetics were determined by the classical titrimetric procedures described by LeBel[6] and Winstein.[28] The solutions were prepared using J. T. Baker Co. reagent grade solvents. Glacial acetic acid containing 1% acetic anhydride was used. The acetone was purified by passing through a column of 4-Å molecular sieve and distilled. Methanol was purified by boiling with magnesium metal followed by distillation. In acetic acid solvolysis, titrations were done by the procedure of LeBel.[6] In acetone–water, titration was performed using sodium methoxide in methanol solution to the green end point of bromothymol blue. The infinity titers for acetolysis were poor (*ca.* 50–60% of the theoretical) and the infinity titers used were calculated using the initial tosylate concentrations. The infinity titers for acetone–water were *ca.* 95% of the theoretical and were used without correction. Tosylate concentrations for both solvolyses were *ca.* 0.03 *N*. The solvolyses were followed to 70% completion in acetic acid and to 75% in acetone–water. The rate constants were obtained by a least-squares analysis of eq 1 with the aid of a

$$kt = \ln \frac{[\mathrm{ROTs}]_\infty - [\mathrm{ROTs}]_0}{[\mathrm{ROTs}]_\infty - [\mathrm{ROTs}]_t} \quad (1)$$

computer. The fits to first-order kinetics were within 5% of the computed straight lines for at least 2 half-lives.

Registry No.—**4**, 24730-85-6; **4** 2,4-DNP, 24730-84-5; **5**, 31444-16-3; **6** 2,3-Cl derivative, 31444-17-4; **6** 3,4-Cl derivative, 31489-86-8; **8**, 31444-18-5; **9**, 31444-19-6; **10**, 31444-20-9; **11**, 31444-21-0; **12**, 31444-22-1; **13**, 31444-23-2; **14**, 31444-24-3; **15**, 31444-25-4; **16**, 22532-37-2; **17**, 31444-27-6; **18**, 31444-28-7; **19** (2-ene), 31444-29-8; **19** (3-ene), 31444-32-3; **22**, 31444-30-1; **23**, 31444-31-2.

Acknowledgment.—Funds generously provided by the National Science Roundation for the purchase of a 100-MHz nmr spectrometer (GP-6940) and a high-resolution mass spectrograph (GP-8509) are gratefully acknowledged.

(28) *Cf.* C. Poulter, E. Friedrich, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 4274 (1970).

Synthesis of *cis*-2-Aza-3-oxo-4-oxabicyclo[4.2.0]octane and *cis*-2-Aza-3-oxo-4-oxabicyclo[4.1.0]heptane

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Internal urethanes, *cis*-2-aza-3-oxo-4-oxabicyclo[4.2.0]octane (**17**) and *cis*-2-aza-3-oxo-4-oxabicyclo[4.1.0]heptane (**7**), have been synthesized. Reactions of these compounds and of their trans counterparts are discussed. The difference in reactivities of several comparable intermediates in the cyclopropane and cyclobutane systems is marked.

Although cyclopropanes[2] and cyclobutanes[3] containing functional groups on C_1 and C_2 have been studied extensively, disubstituted molecules containing different functional groups have received scant notice.[4,5] We have investigated a series of 1,2-disubstituted three- and four-membered rings with known stereochemistry.

Our starting point for each synthesis was the 1,2-diacid **1**[6] or **10**.[7] The cis series was prepared from the anhydride **2** (or **11**) as outlined in Schemes I and II. Reduction of acid chloride ester **13** gave cyclobutane alcohol ester **14**.[8] Although the cyclopropane alcohol ester **4** spontaneously closed to lactone **5**,[4d,e] cyclobutane alcohol ester **14** was somewhat more stable. Maier and Sayrac,[4d] and Kirmse and Dietrich[4e] have prepared lactone **5** by two alternate routes, both procedures involve separation from other products.

While reduction of cyclobutane acid ester **12** to alcohol ester **14** by diborane was accomplished cleanly with formation of little diol as a by-product, reduction of cyclopropane acid ester **3** to alcohol ester **4** was grossly incomplete. Further reduction of the mixture gave 5–10% of diol as well as **4**.

Since reduction of carboxylic acids with diborane involves formation of a triacylborate,[9] intramolecular hydrogen bonding might account for the difference in reduction of **4** and **12**. McCoy[10a,b] has determined the pK_1 of **1b** and Bode[10c] has determined the pK_1 of **10b**. The small difference in acid strength between these two molecules (3.56 *vs.* 4.20) and an observation noted in the reduction of acid esters **4** and **12** indicates that relative solubilities of the intermediate boron compounds are important. While turbidity disappears upon further introduction of diborane with the cyclobutyl compound, a viscous gum precipitates on the sides of the flask and does not redissolve with the cyclopropyl analog.

This difference in the behavior of cyclopropane and cyclobutane systems was amplified in conversion of hydrazides **6** and **16** to cyclic urethanes **7** and **17**. Treatment of cyclobutane alcohol hydrazide **16** with nitrous acid gave 2-aza-3-oxo-4-oxabicyclo[4.2.0]octane (**17**) in good yield under a variety of conditions. In contrast, treatment of cyclopropane alcohol hydrazide **6** with nitrous acid gave large amounts of lactone **5** as well as 2-aza-3-oxo-4-oxabicyclo[4.1.0]heptane (**7**). Urethane **7** could be prepared in satisfactory yield only by rigorous control of both the acidity of the solution and temperature. Formation of lactone **5** was greatly facilitated by addition of ferric chloride, a Lewis acid used to convert azides to isocyanates.[11] The two substituents (hydroxymethyl and azide) which are necessarily eclipsed in the cyclopropane case must be ideally situated so that the hydroxyl group can participate. Lewis acid complexation of the carbonyl oxygen facilitates nucleophilic attack at the carbonyl carbon by the hydroxyl group. Loss of hydrazine from the protonated hydrazide and loss of azide ion from azide leads not to urethane **7** but to lactone **5**. This became most apparent when the azide reverted to lactone **5** even in a chloroform extract which was free of acid. In contrast, the cyclobutane substituents are not eclipsed and formation of lactone **15** presents no serious problem.

Treatment of either urethane **7** or **17** in dioxane with gaseous hydrogen bromide gave bromomethylamine hydrobromide **8** or **18**. Although cyclobutane **18** is stable at room temperature, the cyclopropane analog **8** is unstable even at 5° on prolonged standing.

Ring expansion of urethanes **7** or **17** might occur on treatment with hydrogen bromide. However, the spectroscopic properties of the products **8** and **18** indicate that cyclopropane and cyclobutane rings are intact. The strong absorptions at 8.0 μ in the infrared spectra of the two products can be assigned to a CH_2–Br wagging vibration.[12]

Treatment of **8** or **18** with thallium (or sodium) thiosulfate in either water or methanol gave crude materials

(1) Abstracted from the Ph.D. Dissertations of C. C. Shroff and W. S. Stewart, 1969, and the M.S. Thesis of S. J. Uhm, 1970, Howard University.

(2) J. K. Hecht, J. J. Flynn, and F. P. Boer, *J. Org. Chem.*, **34**, 3645 (1969); F. W. Breitbeil, D. T. Dennerlein, A. E. Fiebig, and R. E. Kuznicki, *ibid.*, **33**, 3389 (1968); S. Sawada, K. Takehana, and Y. Inouye, *ibid.*, **33**, 1767 (1968); O. L. Chapman and R. A. Fugiel, *J. Amer. Chem. Soc.*, **91**, 216 (1969); T. J. Curphey, C. W. Amelotti, T. P. Layloff, R. L. McCartney, and D. B. Priddy, *ibid.*, **91**, 3677 (1969); T. Shono, T. Morikawa, A. Oku, and R. Oda, *Tetrahedron Lett.*, 791, 1964; L. L. McCoy, *J. Amer. Chem. Soc.*, **84**, 2246 (1962), and references therein.

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(4) (a) K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Amer. Chem. Soc.*, **79**, 4994 (1957); (b) W. G. Dauben and G. W. Shaffer, *J. Org. Chem.*, **34**, 2301 (1969); (c) S. J. Rhoads and R. D. Cockroft, *J. Amer. Chem. Soc.*, **91**, 2815 (1969); (d) G. Maier and T. Sayrac, *Ber.*, **101**, 1354 (1968); (e) W. Kirmse and H. Dietrich, *ibid.*, **98**, 4028 (1965).

(5) (a) R. Gelin, S. Gelin, and C. Boutin, *C. R. Acad. Sci.*, **260**, 6393 (1965); (b) P. G. Gassman and K. T. Mansfield, *J. Org. Chem.*, **32**, 915 (1967).

(6) L. L. McCoy, *J. Amer. Chem. Soc.*, **80**, 6568 (1958).

(7) E. C. Coyner and W. S. Hillman, *ibid.*, **71**, 324 (1949); subsequently purchased from Aldrich Chemical Co.

(8) Contrary to expectations considerable amounts of diol were formed when diborane was bubbled through the solution for a longer period (H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 43). The original literature indicates that acid chlorides are relatively inert. See ref 9.

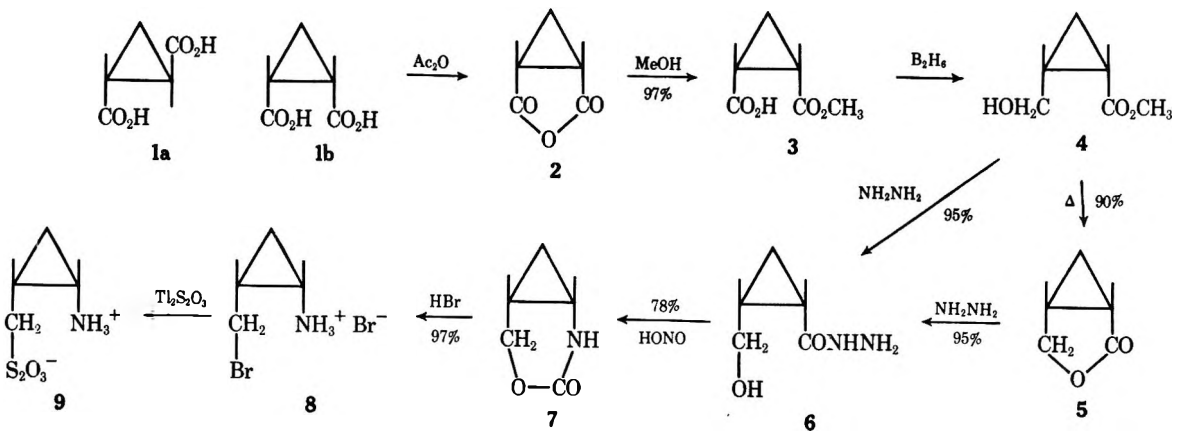
(9) H. C. Brown and W. Korytnyk, *J. Amer. Chem. Soc.*, **82**, 3866 (1960); H. C. Brown and B. C. Subba Rao, *ibid.*, **82**, 681 (1960).

(10) (a) L. L. McCoy, *ibid.*, **85**, 1321 (1963); (b) L. L. McCoy, *J. Org. Chem.*, **30**, 3762 (1965); (c) H. Bode, *Ber.*, **67B**,332 (1934).

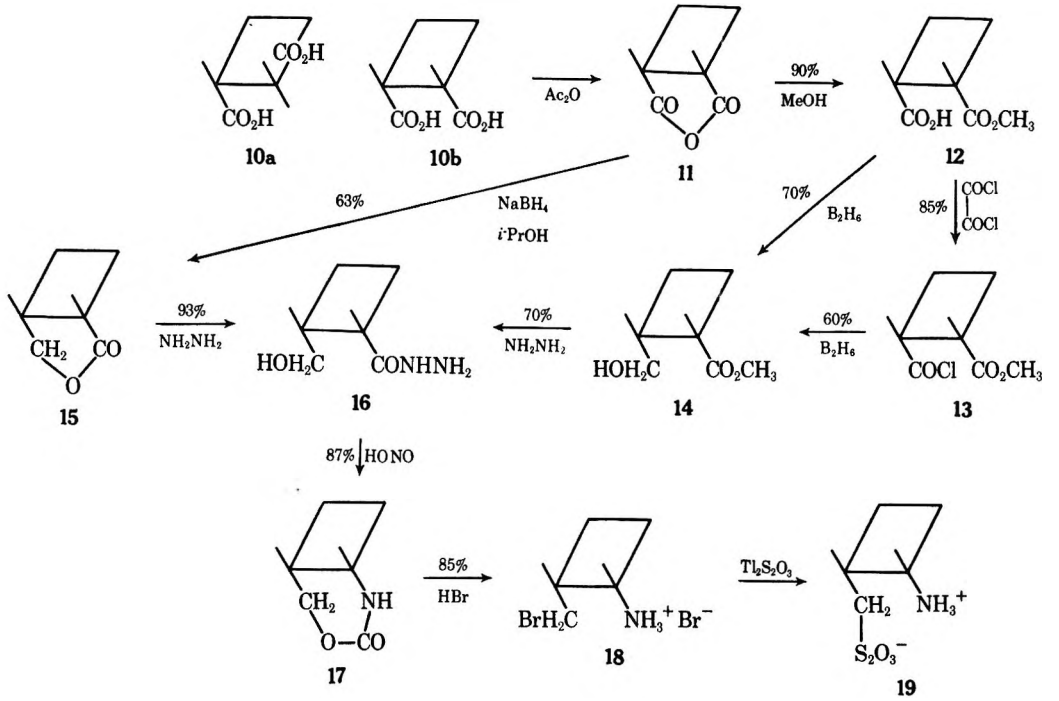
(11) M. S. Newman, *J. Amer. Chem. Soc.*, **70**, 317 (1948); R. A. Coleman and M. S. Newman, *ibid.*, **76**, 4534 (1954).

(12) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1968, p 102.

SCHEME I



SCHEME II



in excellent yield which were spectroscopically consistent with the Bunte salts **9** and **19**. However, repeated attempts at purification did not yield materials giving acceptable analyses, in distinct contrast to the reported stability of Bunte salts.[13] Attempts to prepare the corresponding thiols using sodium sulfide or sodium hydrosulfide gave elimination products instead, as indicated by the appearance of vinyl hydrogens in the pmr spectrum and unsaturation in the infrared spectrum.

Syntheses of the trans series followed the same general procedure (Schemes III and IV). Cyclopropane acid ester **29** was converted to urethane ester **31**. Attempts to reduce this compound to the amine alcohol failed. Although thionyl chloride was used to synthesize the trans acid chloride, this reagent for the cis resulted in epimerization which was circumvented by using oxalyl chloride.[5a]

Cyclobutane acid ester **21** was converted to benzyl urethane alcohol **24** by two alternate routes: **21** → **22** → **23** → **24** and **21** → **25** → **26** → **24**. Treatment of **26** with nitrous acid followed by benzyl alcohol gave the same benzyl urethane alcohol **24** that was obtained by diborane reduction of **23**. However, the presence of an ester group in **22** hindered the conversion of azide to isocyanate, stabilizing the azide in some manner.[14] Both trans urethanes **24** and **27** were treated with gaseous hydrogen bromide in various solvents. Only polymeric material could be isolated. This difference in behavior between internal urethane **17** and the urethane alcohol **24** (or **27**) indicates that formation of bromomethylamine hydrobromide **18** from the internal urethane must occur under conditions which do not facilitate polymerization of the bromoamine. Cleavage of the trans cyclopropyl urethane **31** gave polymeric material as well. An attempted Schmidt reaction on the cis amide acid **32** was unsuccessful.

Carbenoid additions to unsaturated precursors for the synthesis of *cis*- and *trans*-**9** (as well as **33**) were totally unsuccessful.[1,15] Witiak and Lu[16] have recently reported the synthesis of the *cis*- and *trans*-2-(2′-tetra-

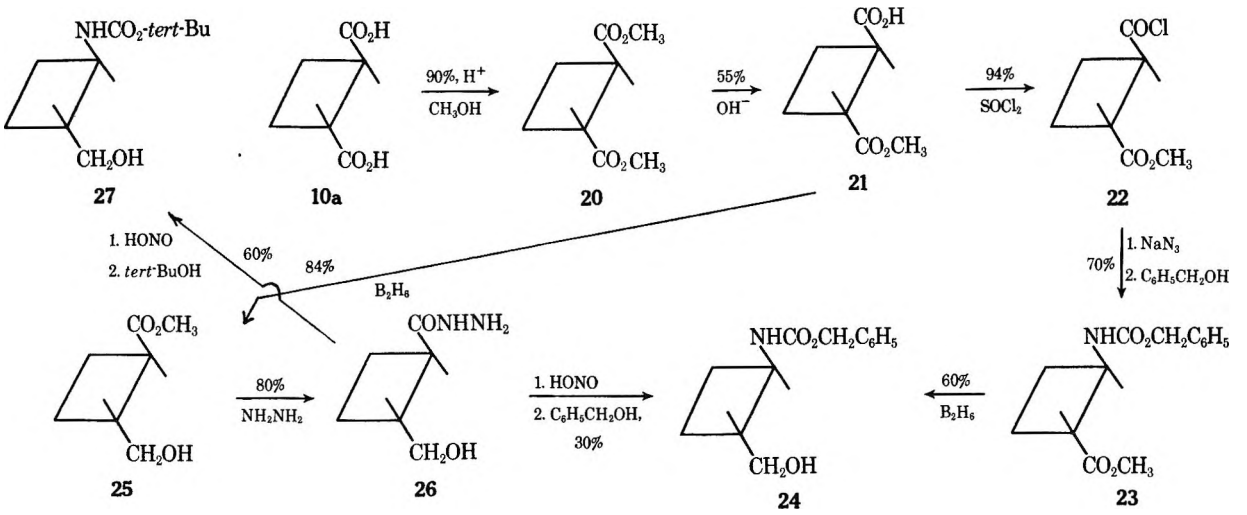
(13) D. L. Klayman and R. J. Shine, *Quart. Rep. Sulfur Chem.*, **3**, 191 (1968).

(14) M. Juang, C. C. Shroff, and W. S. Stewart, unpublished results.

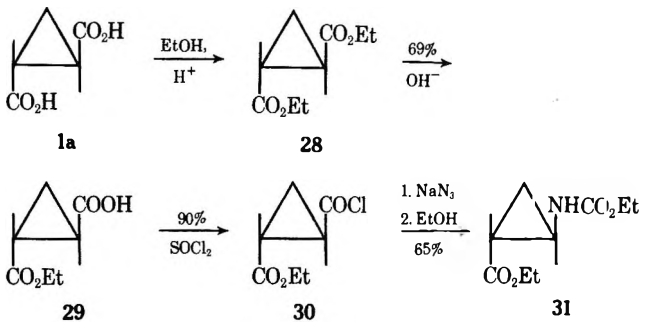
(15) W. E. Parham and S. H. Green, *J. Org. Chem.*, **31**, 1694 (1966) W. E. Parham and J. R. Potoski, *ibid.*, **32**, 275 (1967).

(16) D. T. Witiak and M. S. Lu, *ibid.*, **35**, 4209 (1970).

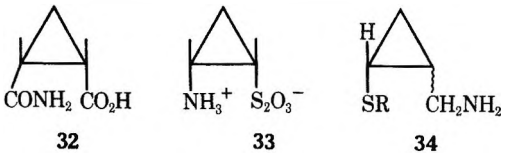
SCHEME III



SCHEME IV



hydropyranylthio)cyclopropylmethylamines (**34a**) by a carbenoid addition. However, they were not able to effect cleavage to the free thiols (**34b**).



a, R = tetrahydropyranyl
b, R = H

Experimental Section

All melting points and boiling points are uncorrected. Melting points were taken on a Thomas-Hoover melting point apparatus in open capillaries. Infrared spectra were taken on a Perkin-Elmer Model 137B Infracord with sodium chloride optics using polystyrene as a calibration. Proton magnetic resonance spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Gas chromatography was done on an Aerograph Model 661 flame ionization instrument using 5 ft × 1/8 in. stainless steel columns. Thin layer chromatography was done on 250-μ silica gel GF plates obtained from Analtech, Inc., Wilmington, Del. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

cis-**Methyl Hydrogen Cyclopropane-1,2-dicarboxylate** (**3**).—Acid anhydride 2[6] (10.0 g, 0.089 mol) in methanol (25 ml) was refluxed for 4 hr. Removal of the methanol gave a thick oily residue which crystallized upon cooling. Digestion in pentane gave colorless crystals (12.5 g, 97%): mp 51–52°; ir (Nujol) 5.77 and 5.87 μ; pmr ($CDCl_3$) δ 1.10–1.55 (m, 1), 1.60–1.82 (m, 1), 2.00–2.30 (m, 2), 3.70 (s, 3), and 11.5 (s, 1).

Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 49.98; H, 5.75.

Methyl *cis*-**2-(Hydroxymethyl)cyclopropanecarboxylate** (**4**) **and** *cis*-**3-Oxa-2-oxobicyclo[3.1.0]hexane** (**5**).—Diborane gas, generated by the dropwise addition of a diglyme solution of sodium borohydride (5.84 g, 0.154 mol) to boron trifluoride etherate (79.6 g, 0.28 mol), was bubbled through a capillary tube into acid ester **3** (10.0 g, 0.069 mol) in ether (150 ml) at room temperature. Generation was continued until dense turbidity appeared and then material precipitated on the walls of the flask giving a clear solution. Hydrolysis with methanol was followed by evaporation giving a colorless liquid which was a mixture of starting material and product. A second reduction under the same conditions gave the desired hydroxy ester plus diol. The diol was separated by alumina column chromatography (ether–methanol) but further purification of the hydroxymethyl ester was hampered by formation of lactone on heating or even on prolonged standing at room temperature. Lactone **5** was obtained in 90% yield (6.13 g) by distillation at 80° (7 mm).

Methyl *cis*-2-(hydroxymethyl)cyclopropanecarboxylate (**4**): ir (neat) 2.82, 5.82, and 9.77 μ; pmr ($CDCl_3$) δ 0.7–1.3 (m, 2), 1.3–2.0 (m, 2), 3.50 (s, 1), 3.68 (s, 3), and 3.60–4.25 (m, 2).

cis-3-Oxa-2-oxobicyclo[3.1.0]hexane (**5**): ir (neat) 5.65[4d,e] and 9.65 μ; pmr (CCl_4) δ 0.6–0.9 (m, 1), 1.0–1.5 (m, 1), 1.6–2.0 (m, 1), 2.0–2.4 (m, 1), and 3.6–4.6 (m, 2).

Anal. Calcd for $C_5H_6O_2$: C, 61.20; H, 6.17. Found: C, 60.83; H, 6.26.

cis-1,2-Di(hydroxymethyl)cyclopropane: ir (neat) 2.97, 8.02, 8.72, and 9.74 μ; pmr (CCl_4) δ 0.0–0.3 (m, 1), 0.4–0.9 (m, 1), 0.9–1.5 (m, 2), 2.9–3.4 (m, 2), 3.7–4.1 (m, 2), and 4.5 (s, 2).

Hydroboration of acid ester **12** was carried out under identical reaction conditions for comparative purposes. The turbidity disappeared upon further bubbling of diborane gas. Hydrolysis with methanol after 1 hr gave little bubbling and a product consisting only of hydroxymethyl ester.

cis-**2-(Hydroxymethyl)cyclopropane Hydrazide** (**6**).—Hydrazine (1.4 g, 97%) in methanol (10 ml) was added to hydroxy ester **4** (3.0 g, 0.023 mol) in methanol (50 ml). After 3 hr of refluxing, the methanol and excess hydrazine were removed at 50°. The crude product was crystallized from ethanol giving 2.84 g (95%) of hydrazide **6**: mp 110–113°; ir (Nujol) 3.18, 6.14, and 6.42 μ; pmr (D_2O) δ 0.9–1.4 (m, 2), 1.5–2.0 (m, 2), 3.73 (m, 2), and 4.77 (s, 4).

Removal of the excess reagent and methanol on a vacuum pump gave a different crystalline form: mp 95–97°; ir (Nujol) 3.05, 6.17, and 6.55 μ. The pmr spectrum was the same as that of the 110° form and recrystallization of the 95° form from ethanol gave the other.

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.14; H, 7.75; N, 21.52. Found: C, 46.12; H, 7.64; N, 21.40.

Treatment of acid ester **3** with hydrazine gave *cis*-1,2-cyclopropane dihydrazide: mp 187–189°; ir (Nujol) 3.03, 6.08, and 6.57 μ; pmr (D_2O) δ 1.00–1.70 (m, 2), 1.90–2.20 (m, 2), and 4.70 (s, 6).

Anal. Calcd for $C_5H_{10}N_4O_2$: C, 37.97; H, 6.37; N, 35.42. Found: C, 37.57; H, 6.27; N, 35.40.

cis-**2-Aza-3-oxo-4-oxabicyclo[4.1.0]heptane** (**7**).—Hydroxy hydrazide **6** (6.00 g, 0.046 mol) was dissolved in water (18 ml), and

sodium nitrite (4.75 g, 0.069 mol) and ether (50 ml) were added to the solution. It was then cooled to just above its freezing point. Hydrochloric acid (11.5 ml, 6 *N*) was added dropwise to the solution from a buret with stirring keeping the temperature below −5°. After the addition was complete, the mixture was transferred to a separatory funnel containing chloroform (300 ml) previously cooled to −10°. After the contents of the separatory funnel had been shaken for 15 min, the aqueous layer was separated and extracted with more chloroform. The combined chloroform was washed with 5% sodium bicarbonate and water, and dried. Concentration of the chloroform layer to half its volume at room temperature was followed by addition of toluene (100 ml) and removal of the remaining chloroform on a rotary evaporator (<40°). Additional toluene (200 ml) was added and the solution digested on a steam bath for 3 hr. Vigorous bubbling occurred above 80°. The solvent was removed and recrystallization from toluene and sublimation gave 3.96 g (78%) of urethane **7**: mp 99.5–100.5°; ir (Nujol) 3.05, 5.95, 6.95, 9.70, and 9.85 μ; pmr ($CDCl_3$) δ 0.5–1.15 (m, 2), 1.15–1.80 (m, 1), 2.7–3.1 (m, 1), 3.85–4.25 (m, 1), 4.50–4.90 (m, 1), and 7.20 (s, 1).

Anal. Calcd for $C_6H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.11; H, 6.04; N, 12.63.

Alternate procedures which added the hydrochloric acid to the hydrazide or ferric chloride to facilitate rearrangement of azide to isocyanate gave large amounts of lactone **5** and low yields of **7**.

Urethane **17** was prepared by the same method. Hydroxy hydrazide **16** (5.00 g, 0.03 mol), sodium nitrite (3.10 g, 0.045 mol), and hydrochloric acid (7.5 ml, 6 *N*) gave an 87% yield (3.80 g) of urethane **17**. The azide readily rearranged to isocyanate in chloroform at room temperature and gave no lactone **15** as a by-product.

***cis*-2-Bromomethylcyclopropylamine Hydrobromide (8).**—Urethane **7** (4.00 g, 0.034 mol) in chloroform (40 ml) was saturated with hydrogen bromide gas giving crystalline material slightly soluble in chloroform. The crude product was washed with small amounts of cold chloroform and dried on a vacuum pump: 7.95 g (97%); mp 124–126°; ir (Nujol) 3.10–4.05, 5.10, 6.25, 8.20, 9.70, 10.48, and 11.80 μ; pmr (D_2O) δ 1.0–1.35 (m, 1), 1.35–1.70 (m, 1), 1.75–2.5 (m, 1), 3.15 (m, 1), 3.50–3.90 (m, 1), 3.90–4.30 (m, 1), and 4.8 (s, 3).

Anal. Calcd for $C_4H_9NBr_2$: C, 20.80; H, 3.93; N, 6.07; Br, 69.20. Found: C, 20.82; H, 3.95; N, 6.24; Br, 69.38.

***cis*-2-Aminocyclopropylmethanethiosulfuric Acid (9).**—Bromomethylamine hydrobromide **8** (0.497 g, 0.002 mol) in methanol (10 ml) was treated with thallous thiosulfate (1.121 g, 0.002 mol) for 3 days at room temperature. The precipitated thallous bromide was filtered (1.197 g, 100%) and the brown filtrate was concentrated on a rotary evaporator. Removal of the aqueous solvent at high vacuum (0.007 mm) gave 0.426 g of crystalline product. Thin layer chromatography (MN 300 Cellulose) showed two spots using a 1-butanol–acetic acid–water (6:1:4) solvent system: R_f 0.415 and 0.895; ir ($CHCl_3$) 3.14, 8.24, 8.37, 9.47, 9.86 and 12.47 μ; pmr (DMSO-d_6) δ 1.1–3.8 (complex), 7.12 (t, 3, J = 51 Hz).

Anal. Calcd for $C_4H_9NS_2O_3$: C, 26.22; H, 4.95; N, 7.64; S, 35.00. Found: C, 13.96; H, 6.00; N, 10.31; S, 24.82; Tl, 0.92.

Further purification was attempted by dissolving the compound in methylene chloride. A white solid precipitated leaving a foul-smelling brown material. Elemental analyses of the white solid indicated that the solvent (methanol) was participating in the reaction. When water was used as the solvent, the crude white solid obtained showed vinyl protons in its pmr spectrum and a peak at 11.0 μ in its ir spectrum indicating that the cyclopropane ring had cleaved. Attempts to prepare the thiol from the corresponding thiosulfate or from the bromide were unsuccessful.

***cis*-Methyl Hydrogen Cyclobutane-1,2-dicarboxylate (12).**—Acid anhydride **11**[7] (10.0 g) in methanol (50 ml) was refluxed for 15 hr. Methanol was removed and the residue distilled: bp 111–112° (3 mm) (11.5 g, 90%); ir (neat) 5.78, 5.9 and 8.3 μ; pmr ($CDCl_3$) δ 2.0–2.8 (m, 4), 3.3–3.6 (m, 2), 3.88 (s, 3), and 11.6 (s, 1).

Methyl *cis*-(2-Chloroformyl)cyclobutanecarboxylate (13).—To acid ester **12** (7.9 g, 0.05 mol) dissolved in dry benzene (50 ml) was added oxalyl chloride (3.2 g, 0.025 mol) and the mixture was refluxed for 4 hr. After removal of the benzene, the precipitated oxalic acid was filtered from the chilled solution and the residue distilled at 60–61° (1 mm) to give **13** (7.5 g, 85%): ir (neat) 5.59, 5.8, and 8.35 μ; pmr (CCl_4) δ 2.0–2.8 (m, 4), 3.2–4.0 (m, 2), and 3.68 (s, 3). The acid chloride was used without further purification for the next step.

Partial Reduction of 11 to *cis*-3-Oxa-2-oxobicyclo[3.2.0]heptane (15).—Sodium borohydride (1.8 g, 0.047 mol) was stirred with 2-propanol (60 ml) for 30 min and anhydride **11** (4.3 g, 0.034 mol), dissolved in warm 2-propanol (40 ml), was added dropwise. The mixture was refluxed for 2.5 hr. After removal of the solvent at reduced pressure, the resultant white solid was decomposed with concentrated hydrochloric acid in ice. The hydrolyzed mixture was stirred 1 hr, heated on a steam bath for 30 min, and extracted with ether. The ether extracts were combined, washed with sodium bicarbonate and water, and dried. Evaporation of ether gave lactone **15** (2.4 g, 63%): bp 63–64° (1 mm) [lit.[5a,b] 108° (17 mm), 74° (1.5 mm)]; ir (neat) 2.87, 5.68, and 8.7 μ; pmr (CCl_4) δ 1.1–2.75 (m, 4), 2.75–3.6 (m, 2), and 3.8–4.5 (m, 2).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 63.98; H, 7.17.

Diborane Reduction of 13.—The procedure used was that described for preparing **4**. Acid chloride ester **13** (3.52 g, 0.02 mol) gave **14** (1.7 g, 60%): bp 70–72° (1 mm); ir (neat) 2.91, 5.79, and 8.38 μ; pmr (CCl_4) δ 1.7–2.4 (m, 4), 2.6–3.0 (m, 1), 3.0–3.3 (m, 1), 3.50 (d, 2, J = 6 Hz), 3.6 (s, 3), and 4.2 (broad absorption, 1).

Diborane Reduction of 12.—Acid ester **12** (3.2 g, 0.02 mol) was reduced by the method described for **4**. Removal of methanol gave **14** (2.0 g, 70%): bp 75–76° (1 mm); the ir and pmr spectra were identical with those of the product obtained in the preceding experiment.

***cis*-(2-Hydroxymethyl)cyclobutanecarboxylic Acid Hydrazide (16) from 14.**—Hydroxy ester **14** (1.44 g, 0.01 mol) was treated as **4** was converted to **6**. Recrystallization from ethanol gave **16** (1.0 g, 70%): mp 114–115°; ir (Nujol) 3.05, 5.99, and 6.10 μ; pmr (DMSO-d_6) δ 1.50–2.25 (m, 4), 2.25–2.75 (m, 1), 2.75–3.25 (m, 1), 3.48 (d, 2, J = 7 Hz), and 3.7–4.3 (broad absorption, 4).

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 50.07; H, 8.18; N, 19.23.

***cis*-(2-Hydroxymethyl)cyclobutanecarboxylic Acid Hydrazide (16) from 15.**—As described in the conversion of **4** to **6**, lactone **15** (3.36 g, 0.03 mol) and hydrazine hydrate (1 ml) in anhydrous *n*-butyl alcohol (50 ml) were refluxed for 8 hr. A similar work-up gave **16** (4.0 g, 93%); ir and pmr spectra were identical with those of the product obtained in the preceding experiment. Lower boiling alcohols were much less effective as solvents.

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 49.91; H, 8.59; N, 19.20.

***cis*-2-Aza-3-oxo-4-oxabicyclo[4.2.0]octane (17).**—Hydroxy hydrazide **16** (2.5 g, 0.017 mol) was converted to urethane **17** in the same manner as **6** was converted to **7**. Removal of toluene gave crystalline urethane **17** upon chilling (1.3 g, 59%): mp 89.5–90.5°; ir (Nujol) 3.14, 5.88, and 5.95 μ; pmr ($CDCl_3$) δ 1.75–2.63 (m, 4), 2.65–3.15 (m, 1), 3.70–4.15 (m, 1), 4.28 (d, 2, J = 5 Hz), and 6.9–7.5 (broad absorption, 1).

Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.59; H, 7.03; N, 11.08.

***cis*-2-Bromomethylcyclobutylamine Hydrobromide (18).**—Urethane **17** (1.27 g, 0.01 mol) was converted to **18** by the same method as **7** was converted to **8** except that dioxane was used as solvent. The crystalline residue was recrystallized from chloroform to give **18** (2.1 g, 85%): mp 169.5–170.0°; ir (Nujol) 3.1–4.2, 5.42, 8.0, and 14.95 μ; pmr (D_2O) δ 1.50–2.5 (m, 4), 2.85–3.40 (m, 1), 3.74 (d, 1, J = 7.0 Hz), 3.74 (d, 1, J = 9.0 Hz), 3.95–4.30 (m, 1), and 4.60–4.85 (s, 3).

Anal. Calcd for $C_5H_{11}NBr_2$: C, 24.51; H, 4.53; N, 5.72; Br, 65.24. Found: C, 24.19; H, 4.43; N, 5.85; Br, 63.43.

***cis*-2-Aminocyclobutylmethanethiosulfuric Acid (19).**—Bromomethylamine hydrobromide **18** (1.22 g, 0.005 mol) dissolved in distilled water (25 ml) and thallium (ous) thiosulfate (2.6 g, 0.005 mol) were refluxed for 36 hr with stirring. The contents of the flask were filtered to remove the thallium bromide precipitate (2.84 g, 100%), chilled overnight, and refiltered. The filtrate was freeze-dried yielding a white, crystalline product (1.0 g, 100%), mp 172–173° dec. The product gave a positive test for nitrogen and sulfur[17] and a negative test for bromine:[17]

(17) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Wiley, New York, N. Y., 1966, pp 1041, 1042.

ir (Nujol) 3.1–4.35, 5.0, 6.16, and 9.75 μ; pmr (D_2O) δ 1.7–2.7 (m, 4), 3.0–3.6 (m, 1), 3.38 (d, 1, J = 6.0 Hz), 3.41 (d, 1, J = 9.0 Hz), 3.9–4.3 (m, 1), and 4.7 (s, 3).

Analyses were consistently low in carbon, hydrogen, and sulfur even after purification by tlc. A large ash content was always observed but analysis showed no thallium present.

trans-**Dimethylcyclobutane-1,2-dicarboxylate** (**20**).—Diacid **10a**[7] (50.0 g, 0.34 mol), anhydrous methanol (250 ml), and concentrated sulfuric acid (1 ml) were refluxed with stirring for 35 hr, allowed to cool, and distilled giving 52.2 g (90%) of a colorless liquid: bp 74° (3 mm) [lit.[18] 105–107° (13 mm)]; ir (neat) 5.75 and 8.0 μ; pmr ($CDCl_3$) δ 3.68 (s, 6), 3.41 (m, 2), and 2.17 (m, 4).

trans-**Methyl Hydrogen Cyclobutane-1,2-dicarboxylate** (**21**).—Anhydrous methanol (100 ml) and **20** (43.0 g, 0.25 mol) were heated to reflux and a solution of sodium hydroxide (10.4 g, 0.26 mol) in water was added over a period of 2 hr. The solution was cooled and concentrated at 15-mm pressure. The residue was diluted with water and concentrated again for a short period of time, and the aqueous solution was extracted with ether. The aqueous solution was then acidified to pH 3, extracted with ether, dried, concentrated, and distilled under reduced pressure to give 22.0 g (55%) of colorless liquid **21**: bp 106–108° (1 mm); ir (neat) 3.2, 5.70, 5.80, and 7.9 μ; pmr ($CDCl_3$) δ 2.20 (m, 4), 3.45 (m, 2), 3.68 (s, 3), and 11.4 (s, 1).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.90; H, 6.40.

Methyl *trans*-**2-(Chloroformyl)cyclobutanecarboxylate** (**22**).—Acid ester **21** (10.8 g, 0.062 mol) and thionyl chloride (18.0 g, 0.15 mol) were stirred and heated under reflux for 2 hr. The reaction mixture was distilled at atmospheric pressure to remove the excess thionyl chloride and distilled under reduced pressure to give 11.8 g (94%) of acid chloride **22**: bp 52° (1 mm); ir (neat) 5.50, 5.73, and 8.0 μ; pmr ($CDCl_3$) δ 2.30 (m, 4), 3.45 (m, 1), 3.70 (s, 3), and 3.85 (m, 1).

Anal. Calcd for $C_7H_9O_3Cl$: C, 47.72; H, 5.11. Found: C, 47.54; H, 5.15.

Methyl *trans*-**2-(*N*-Carbobenzyloxyamino)cyclobutanecarboxylate** (**23**).—Acid chloride **22** (11.3 g, 0.065 mol) was dissolved in dry acetone and cooled to 0°. Sodium azide (6.6 g, 0.01 mol) dissolved in water was added dropwise, and the resulting mixture was stirred for 2 hr at 0°, poured into ice–water, and extracted with ether. The ethereal extracts were dried, filtered, and concentrated. The oily residue that remained was refluxed in 100 ml of dry toluene with 10 ml of benzyl alcohol for 4 days. The solution was concentrated and chromatographed on alumina. An 8:2 solution of petroleum ether–methylene chloride eluted 3.2 g of pure urethane ester **23**. All subsequent fractions contained benzyl alcohol as the principal contaminant. A total of 13.5 g (70%) of **23** was obtained by repeated chromatography: ir (neat) 2.9, 5.75, and 7.5 μ; pmr ($CDCl_3$) δ 2.0 (m, 4), 3.0 (m, 1), 3.55 (s, 3), 4.37 (m, 1), 5.0 (s, 1), 5.85 (broad s, 1), and 7.2 (s, 5).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.00; H, 6.67; N, 5.14.

Diborane Reduction of 23.—Urethane ester **23** (10.0 g, 0.036 mol) was reduced with diborane as in the preparation of **4**. Crystallization from cyclohexane–methylene chloride gave 5.1 g (60%) of white urethane **24**: mp 82–83°; ir (Nujol) 2.9, 5.87, and 7.80 μ; pmr ($CDCl_3$) δ 2.0 (m, 4), 3.55 (m, 4), 3.75 (s, 1), 5.15 (s, 2), 5.4 (s, 1), and 7.4 (s, 5).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.40; H, 7.54; N, 6.20.

trans-**Methyl 2-Hydroxymethylcyclobutanecarboxylate** (**25**).—Acid ester **21** (10.0 g, 0.062 mol) was reduced with diborane as in the preparation of **4**. Distillation under reduced pressure gave 7.6 g (84%) of a colorless liquid: bp 81–82° (1 mm); ir (neat) 2.9, 5.75 and 8.0 μ; pmr ($CDCl_3$) δ 1.95 (m, 4), 2.85 (m, 2), 3.5 (d, 2, J = 5 Hz), 3.6 (s, 3), and 3.9 (s, 1).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.06; H, 8.40.

trans-**2-Hydroxymethylcyclobutane Hydrazide** (**26**).—Hydroxy ester **25** (5.0 g, 0.034 mol) was treated as **4** was converted to **6**. The resulting oily material was crystallized from absolute ethanol–ether to give 4.0 g (80%) of a white solid: mp 88–89°; ir (KBr) 3.0 and 6.1 μ; pmr (D_2O) δ 1.9 (m, 4), 2.7 (m, 2), 3.55 (d, 2, J = 6 Hz), and 4.65 (s, 4).

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 50.17; H, 8.57; N, 19.58.

trans-**2-Hydroxymethyl(*N*-carbobenzyloxy)cyclobutylamine** (**24**).—Hydroxy hydrazide **26** (2.5 g, 0.017 mol) was converted to azide in the same manner as **6** was converted to **7**. The ethereal solution of azide alcohol was added dropwise to refluxing toluene containing 2.0 g (0.02 mol) of benzyl alcohol and the ether was allowed to distill. After removal of ether, the resulting solution was refluxed, with stirring, for 12 hr. Concentration of the cooled reaction mixture and crystallization of the remaining oil from cyclohexane–methylene chloride gave 1.3 g (30%) of a crystalline white urethane **24**, mp 82–83°. This material was identical with the product obtained from the diborane reduction of **23**, admixture mp 82–83°.

trans-**2-Hydroxymethyl(*N*-carbo-*tert*-butoxy)cyclobutylamine** (**27**).—The procedure used was identical with that employed in the preparation of **24** including quantities of materials, except that *tert*-butyl alcohol was used in place of benzyl alcohol. The crude product was purified by sublimation at 60° (1 mm) to give 2.0 g (60%) of a white urethane **27**: mp 69–70°; ir (Nujol) 2.9, 5.95, 6.5, and 7.75 μ; pmr ($CDCl_3$) δ 1.4 (s, 9), 1.9 (m, 4), 3.5 (d, 2, J = 7 Hz), 4.85 (s, 1), and 5.0 (broad s, 1).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.43; H, 9.78; N, 6.87.

Reaction of 24 with Hydrogen Bromide.—Gaseous hydrogen bromide was passed into a solution of **24** (1.0 g, 0.004 mol) in anhydrous, purified chloroform (75 ml) for 30 min. The resulting mixture was stirred overnight at room temperature. The chloroform solution was decanted from the semisolid that remained (0.5 g) and the combined chloroform extracts were concentrated. A tlc (chloroform–ether, 1:1) indicated two components, the R_f values of both being different from that of the starting material. The ir and pmr spectra indicated a mixture of benzyl bromide and *trans*-2-bromomethyl(*N*-carbobenzyloxy)-cyclobutylamine. No attempt was made to further separate or characterize these materials. Similar reactions were attempted using other solvents. The results in each case were identical with those just described.

trans-**Ethyl Hydrogen Cyclopropane-1,2-dicarboxylate** (**29**).—Partial hydrolysis of diester **28** by the method of Wiberg[4a] gave the title compound in 69% yield: mp 56–57° (lit.[4a] 58–60°); ir (CCl_4) 2.7–3.3, 5.76, 5.88, and 8.35–8.45 μ; pmr ($CDCl_3$) δ 1.4 (t, plus m, 5), 2.25 (m, 2), 4.3 (q, 2, J = 7 Hz), and 11.7 (s, 1).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.87; H, 6.28.

trans-**2-Carbethoxycyclopropanecarboxylic Acid Chloride** (**30**).—To thionyl chloride (11.9 g, 0.02 mol) was added acid ester **29** (3.2 g, 0.02 mol) and the solution was refluxed for 4 hr. Excess thionyl chloride was removed and the residue distilled at 65–66° (1 mm) giving 3.15 g (90%) of acid chloride **30**: ir (neat) 5.62, 5.8, 8.3, and 10.05 μ; pmr ($CDCl_3$) δ 1.3 (t, 3, J = 7 Hz), 1.72 (m, 2), 2.53 (m, 2), and 4.18 (q, 2, J = 7 Hz). The acid chloride was used without further purification for the next step.

Ethyl *trans*-**(2-*N*-Carbethoxyamino)cyclopropanecarboxylate** (**31**).—The acid chloride (1.76 g, 0.01 mol) was converted to azide by the same method as used for **23**. The crude azide was added to toluene and heated until nitrogen evolution ceased (about 2 hr). Addition of ethanol was followed by refluxing and solvent was removed. The oily residue solidified upon cooling. Recrystallization from chloroform–cyclohexane or sublimation at 100° (1 mm) gave urethane **31** (1.3 g, 65%): mp 59.5–60.0°; ir (Nujol) 3.05, 5.85, 5.95, 6.56, and 8.5 μ; pmr ($CDCl_3$) δ 1.0–1.5 (m plus t, 8, J = 7 Hz), 1.5–1.9 (m, 1), 2.9–3.3 (m, 1), 3.9–4.4 (overlapping q, 4, J = 7 Hz), and 5.6 (s, 1).

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.79; H, 7.33; N, 7.23.

cis-**2-Amidocyclopropanecarboxylic Acid** (**32**).—To acid anhydride **2**[6] (7.5 g, 0.067 mol) was added ammonium hydroxide (50 ml) over a period of 1 hr with cooling. The excess ammonia was removed on a steam bath under a stream of nitrogen. Concentrated hydrochloric acid was added until precipitation was complete and the flask was cooled in a refrigerator. The amide acid **32** was filtered, washed with water, and recrystallized from hot water. The yellowish white product (4.3 g, 50%) had mp 179.5–180°; ir (Nujol) 2.95, 5.80, and 6.0 μ; pmr (DMSO-d_6) δ 0.7–1.55 (m, 2), 1.65–2.20 (m, 2), 6.7–7.4 (s, 1), and 7.4–8.0 (s, 2).

Anal. Calcd for $C_6H_7NO_3$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.63; H, 5.30; N, 10.71.

(18) R. Kuhn and A. Wasserman, *Helv. Chim. Acta*, **11**, 600 (1928); H. Bode, *Ber.*, **67**, 332 (1934).

Attempted Hofmann Degradation of 32.—To a mixture of sodium hydroxide (14.0 g, 0.35 mol) and **32** (6.45 g, 0.05 mol) in an ice–water mixture (50 g) was added bromine (16.0 g, 0.1 mol) dropwise over 30 min. After heating the reaction mixture on a steam bath until it was clear, hydrochloric acid was added and the mixture was extracted three times with ether. Removal of ether gave a negligible residue as did continuous extraction of the aqueous layer.

Registry No.—**3**, 31420-47-0; **4**, 31443-73-9; **5**, 4606-09-1; **6**, 31420-49-2; **7**, 31420-50-5; **8**, 31420-51-6; **9**, 31392-62-8; **12**, 31420-52-7; **13**, 31420-53-8; **14**, 31420-54-9; **15**, 7687-28-7; **16**, 31420-56-1; **17**, 31420-57-2; **18**, 31420-58-3; **19**, 31392-63-9; **20**, 7371-67-7; **21**, 31420-60-7; **22**, 31443-74-0; **23**, 31420-61-8; **24**, 31420-62-9; **25**, 31420-63-0; **26**, 31420-64-1; **27**, 31420-65-2; **29**, 31420-66-3; **30**, 17868-78-9; **31**, 31420-68-5; **32**, 15982-33-9; *cis*-1,2-di(hydroxymethyl)-cyclopropane, 2345-68-8; *cis*-1,2-cyclopropane dihydrazide, 2374-08-5.

Acknowledgment.—We thank the U. S. Army Research and Development Command, Office of the Surgeon General, Contract Number DA-49-193-MD-3030, for their generous support of this work.

The Synthesis of 2,5- and 2,6-Bis(bromomethyl)-1,4-diphenylpiperazines and Their Conversion into 2,5-Diphenyl-2,5-diazabicyclo[2.2.2]octane[1]

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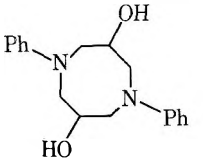
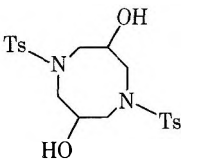
Treatment of *cis*-1,5-diphenyl-3,7-dihydroxyoctahydro-1,5-diazocine (**1**) with phosphorus tribromide yielded a mixture of *cis*-2,6-bis(bromomethyl)-1,4-diphenylpiperazine (**4**) and *cis*-2,5-bis(bromomethyl)-1,4-diphenylpiperazine (**5**). The structures of **4** and **5** were confirmed by conversion to the corresponding dimethyl-1,4-diphenylpiperazines (**6** and **7**) by lithium aluminum hydride. Compounds **6** and **7** were synthesized from *cis*-2,5- and *cis*-2,6-dimethylpiperazines. Both **4** and **5** on treatment with magnesium in tetrahydrofuran were converted to 2,5-diphenyl-2,5-diazabicyclo[2.2.2]octane (**8**). The interconversion of **4** and **5** is discussed.

As part of a study of the chemistry of 3,7-disubstituted 1,5-diphenyloctahydro-1,5-diazocines, we have investigated the reaction of 1,5-diphenyl-3,7-dihydroxyoctahydro-1,5-diazocine (**1**) with phosphorus tribromide. The synthesis of **1** was first reported by Gaertner,[2] but the question of the stereochemistry of the hydroxyl groups was not settled. Thin layer chromatography on silica gel of **1** as it crystallized from the reaction mixture shows it to be essentially homogeneous, with only a trace of a second, faster moving component. Recrystallization from ethyl acetate–methanol gives a product homogeneous to thin layer chromatography under a variety of conditions. Paudler and coworkers[3] have presented arguments for distinguishing the cis and trans isomers of 1,5-bis(*p*-toluenesulfonyl)-3,7-dihydroxyoctahydro-1,5-diazocine (**2**) by the separation of the nmr resonances of the ring methylene hydrogens. Thus, with their systems, it would appear that the ring methylene hydrogens are more nearly magnetically equivalent in the trans isomer than in the cis isomer, and with both isomers in hand, they assign the stereochemistry on this basis. Although the methylene signals of **1** show a comparable separation with *cis*-**2**, 0.89 *vs.* 0.80 ppm, an examination of both Dreiding and CPK space filling models show that the *N*-phenyl groups of **1** can cause a similar degree of magnetic nonequivalence of the ring methylene hydrogens in a variety of conformations of both cis and trans isomers. Without isolation of a second isomer, we hesitate to assign stereochemistry on the basis of Paudler's criteria alone. However, the separation of the methylene resonances together with the stereochemistry of the dibromo derivative discussed below lead us to the conclusion that we are dealing with the cis isomer of **1**.



1



2

Treatment of **1** with phosphorus tribromide at 115° yields, after hydrolysis with water, a compound, $C_{18}H_{21}Br_3N_2$ (**3**), which, from its infrared spectrum, was deduced to be a hydrobromide salt. The nmr spectrum of **3** was not that to be expected from a dibromodiazocine, but clearly indicated its structure to be a bis(bromomethyl)-1,4-diphenylpiperazine monohydrobromide. The most significant signal in the spectrum of **3** was a doublet at δ 2.4 (4 H) which was assigned to the methylene hydrogens of the bromomethyl groups, split by the tertiary hydrogen (H_X). The signal from the tertiary hydrogens appeared as a broad multiplet at δ 4.5 (2 H). Irradiation of the signal at δ 4.5 collapsed the signal at δ 2.4 to a singlet. The remaining signals of the ring methylenes appeared as the AM part of an AMX system from δ 3 to 4.

Neutralization of **3** with ammonium hydroxide yielded a solid which upon recrystallization gave a compound $C_{18}H_{20}N_2Br_2$, mp 132–134°.[4] Concentration of the mother liquor from the recrystallization gave an isomeric compound **5**, mp 117–119°.

Compounds **4** and **5** were characterized as bromomethylpiperazines by their identical mass spectra, which showed a peak for the loss of a CH_2Br fragment from the molecular ion, and by their reduction to the

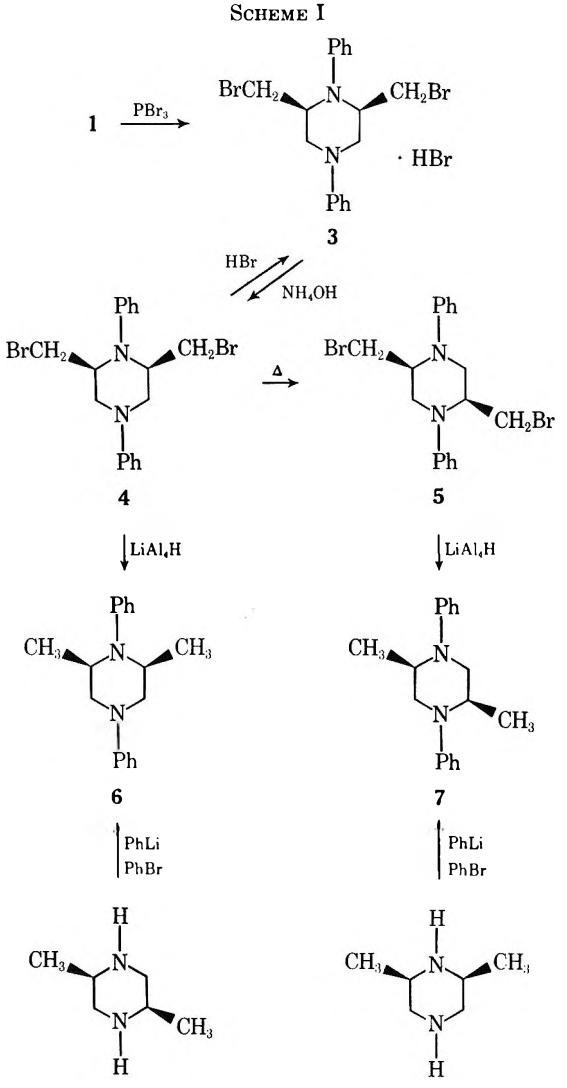
(1) (a) This research was supported, in part, by Public Health Service Grant GM-13117. (b) Presented in part at the First International Conference on Heterocyclic Chemistry, Albuquerque, N. M., June 1967. (c) Abstracted in part from the Ph.D. thesis of J. J. W., University of Wyoming, Aug 1968.

(2) V. R. Gaertner, *Tetrahedron Lett.*, 141 (1964).

(3) (a) W. W. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.*, **31**, 277 (1966); (b) W. W. Paudler, A. G. Zeiler, and G. R. Gapski, *ibid.*, **34**, 1001 (1969).

corresponding dimethylpiperazines with lithium aluminum hydride.[4] The major product from the reduction of **4** was identical in its nmr and mass spectrum, and vpc retention time, with *cis*-2,6-dimethyl-1,4-diphenylpiperazine (**6**). The lithium aluminum hydride reduction product of **5** was likewise shown to be *cis*-2,5-dimethyl-1,4-diphenylpiperazine (**7**). Compounds **6** and **7** were prepared by the diphenylation of the corresponding dimethylpiperazines. When an ether solution of **4** was treated with gaseous hydrogen bromide, **3** was formed. These reactions are summarized in Scheme I.

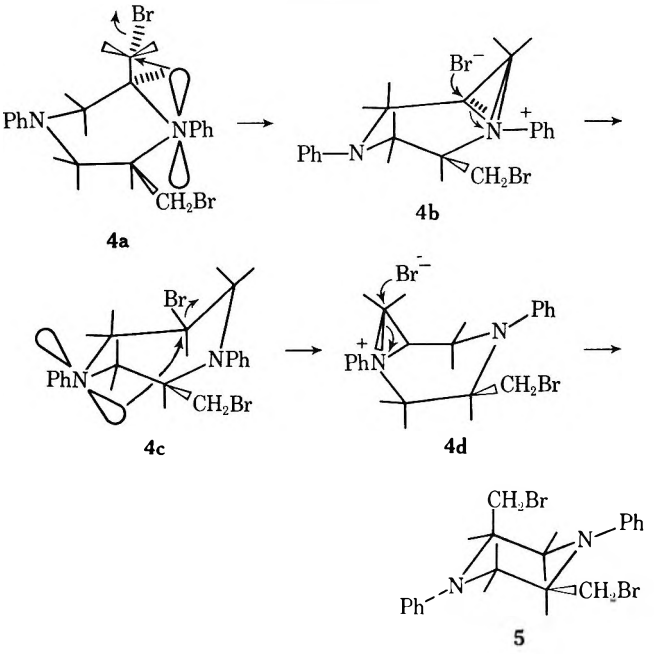
SCHEME I



Thus, **3** must be the monohydrobromide salt of *cis*-2,6-bis(bromomethyl)-1,4-diphenylpiperazine (**4**). When **4** was recrystallized from ethyl acetate–methanol, **5** was found in the mother liquors. Also, when **4** was placed in a sublimator and heated to 170°, **5** formed in the melt. Since only one hydrobromide salt was isolated from the reaction of **1** with PBr_3, the conclusion is that **4** is the major product of the reaction and that **5** results from the thermal rearrangement of **4** to **5**. Using arguments analogous to Paudler's,[3b] **4** would result from the ring contraction of **1** by way of intermediate aziridinium ions. Assuming a similar mechanism, the cis stereochemistry of the bromomethyl groups in **4** should result from a cis configuration of the hydroxy groups in **1**.

A reasonable mechanism for the rearrangement of **4** to **5** also involving aziridinium ions is shown in Scheme II. An analysis of the reaction pathway using Dreiding

SCHEME II

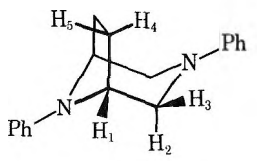


models shows that, if **4** assumes a twist–boat conformation, **4a**, then the electron pair on nitrogen is most favorably located for back-sidedis placement of a bromine atom from a pseudoaxial bromomethyl group. A reasonable population of this conformation would be expected because of the considerable nonbonded interactions between the cis-diequatorial bromomethyl groups and the 1-*N*-phenyl ring in the chair conformation. Displacement in this conformation leads to formation of the *cis*-aziridinium ion **4b**, which opens to the *cis*-diazepine **4c**. Ring contraction of this structure would be expected to proceed in a stereospecific manner through the aziridinium ion **4d** to give **5**.[3b]

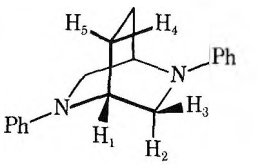
As part of an investigation of the chemistry of **4** and **5**, an attempt was made to prepare their corresponding Grignard reagents by treatment with magnesium in tetrahydrofuran. In an experiment designed to determine if any rearrangements had taken place, the Grignard solution from **4** was hydrolyzed with aqueous ethanol, and the major product (about 80%) was isolated by trapping from the gas chromatograph. The isolated product contained no bromine but was not the dimethylpiperazine **6**, since it had a mass spectrometric molecular weight of 264. The mass spectrum also showed no M − 15 peak, and the ultraviolet spectrum showed no unsaturation. These observations, coupled with the nmr spectrum which showed, in addition to the signals from aromatic hydrogens, three symmetrical multiplets centered at δ 4.34 (2 H), 3.26 (4 H), and 2.00 (4 H), led to the conclusion that the product was either 3,8-diphenyl-3,8-diazabicyclo[3.2.1]octane (**9**) or 2,5-diphenyl-2,5-diazabicyclo[2.2.2]octane (**8**).

(4) We originally reported **4** and **5** as dibromodiazocines and proposed the ring contraction upon the reduction with lithium aluminum hydride: D. A. Nelson and J. J. Worman, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstract 85. A subsequent report by Paudler,[3b] together with the results presented here, show that the ring contraction must occur on treatment of **1** with PBr_3.

An analysis of the nmr spectrum led to the conclusion that the product has structure **8**. The signal at δ 4.34 is assigned to the resonance from H_1. This



9



8

hydrogen is most deshielded since it lies in the plane of the aromatic ring. The signal at δ 3.26 is assigned to H_2 and H_3, and that at δ 2.00 to H_4 and H_5. An examination of Dreiding models of **8** and **9** shows that in **8** H_1 has dihedral angles with H_2, H_3, H_4, and H_5 all equal to 60°. Thus values of J_{12}, J_{13}, J_{14}, and J_{15} would all be expected to be very close. At 100-Hz sweep width, the signal at δ 4.34 appears as a broadened quintet, J = 2.3 Hz, which would be expected for H_1 split by four equivalent couplings. The broadening is attributed to the nitrogen atom and possible long-range couplings. Irradiation of the signal at δ 3.26 collapsed the signal at δ 4.34 to a triplet, J = 2.3 Hz. Upon irradiation of the signal at δ 4.34, the signal at δ 3.26 (H_2, H_3) collapsed to an AB quartet, J_{23} = 11 Hz. In the [3.2.1] structure **9** with the six-membered ring in the boat conformation, $J_{H_{12}} \neq J_{H_{14}}$ and $J_{H_{13}} \neq J_{H_{15}}$. With the six-membered ring in the chair conformation, $J_{H_{12}} = J_{H_{13}}$, but $J_{H_{14}} \neq J_{H_{15}}$. In neither case would the H_1 and H_2, H_3 resonances be expected to have the observed patterns. As confirmation of these conclusions, the nmr spectra of 3,8-dibenzyl-3,8-diazabicyclo[3.2.1]octane (**12**)[5] and 2,5-diazabicyclo[2.2.2]-octane dihydrochloride (**13**)[6] were recorded. The H_{23} portion of the spectrum of **10** showed $J_{H_{12}}$ = 1.8, $J_{H_{13}}$ = 2.5 Hz. The H_{23} portion of the spectrum of **11** showed a pattern very similar to that of **8**, with $J_{12} = J_{13}$ = 2.3 Hz.

When **5** was treated with magnesium in tetrahydrofuran, **8** was also formed as the major product. This observation serves to confirm the structure of **8**, and since this can be considered as an internal Grignard coupling reaction it also confirms the structure **5** as the *cis*-2,5-bis(bromomethyl)piperazine. The formation of **8** from **4** must also involve a rearrangement of **4** to **5**, followed by coupling. In refluxing tetrahydrofuran, the solvent of the reaction of **4** with magnesium, **4** was not converted to **5**. Therefore, the organometallic reagent must play some role in the isomerization. Compound **8** was also observed as a minor product in the reduction of both **4** and **5** with lithium aluminum hydride, and as the major product when a tetrahydrofuran solution of **4** was treated with methyllithium. A possible pathway for the conversion of **4** to **8** may involve anionic intermediates. A detailed study of this mechanism is now in progress.

Experimental Section

Infrared spectra were recorded on a Beckman IR-10 as Nujol mulls, KBr pellets, or neat samples on KBr plates. The Perkin–Elmer 621 was used to record the infrared spectrum of 2,5-diphenyl-2,5-diazabicyclo[2.2.2]octane (**8**) as a neat sample on KBr plates. Ultraviolet spectra for the diazocines were recorded on a Beckman DB spectrophotometer using 1-cm cells. The mass spectra were obtained from a CEC-21-103-C mass spectrometer or a Varian Mat CH-5 mass spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian HA-100 instrument. The δ values are reported with respect to internal TMS. Gas chromatographic analyses were performed on an Aerograph 1520 using a thermal conductivity detector and helium as the carrier gas. The injector temperature was maintained at 290° and the detector was maintained at 300°. The oven temperature ranged from 185 to 255° depending on the number and types of components involved. Analyses were carried out on $^1/_8$-in. columns and preparative work was done using $^3/_8$-in. columns.

	Dimensions	Solid support	Liquid
Column A	$^1/_8$ in. by 5 ft stainless steel	Gas-Chrom P or ABS Anakrom	10% SE-30
Column B	$^3/_8$ in. by 5 ft aluminum	ABS Anakrom	10% SE-30

Boiling points are uncorrected (prevailing atmospheric pressure approximately 585 mm). The melting points were obtained using a Thiele tube containing paraffin oil and are uncorrected. Elemental analyses were performed by Huffman Laboratories, Wheat Ridge, Colo., and by Schwartzkopf Laboratories, New York, N. Y.

1,5-Diphenyl-3,7-dihydroxyoctahydro-1,5-diazocine (**1**).—The procedure described here represents a modification of the ones described by Gaertner.[7] To 8.00 g (0.039 mol) of *N*,*N*-bis(2,3-epoxypropyl)aniline[8] in 50 ml of methanol was added 3.72 g (0.039 mol) of aniline. The reaction was stoppered and allowed to stand at room temperature. After 5 days a white solid appeared, and after 11 days this was filtered and dried. After the mother liquor from the above sample was allowed to stand at room temperature for an additional 12 hr, a large mass of white crystals formed: mp 208–214° after two recrystallizations from methanol (lit.[2] mp 208–213°); yield 2.30 g (19.8%); uv max ($CH_3C{\equiv}N$) 250 nm (ϵ 27,000); ir (KBr) 3360, 2990, 1620, 1581, 1520, 1490, 1445, 1390, 1370, 1330, 1279, 1262, 1225, 1167, 1099, 1060, 1034, 1000, 905, 882, 860, 740, 690, 665 cm^{-1}; nmr (acetone-d_6) δ 7.1 (m, 4), 6.5 (m, 6), 4.3–2.8 (m, 12); mass spectrum (70 eV) *m/e* (rel intensity) 298 (40), 280 (22), 253 (48), 174 (35), 148 (20), 132 (28), 120 (100).

Reaction of 1 with Phosphorus Tribromide (PBr_3). Preparation of *cis*-2,6-Bis(bromomethyl)-1,4-diphenylpiperazine (**4**).—To 1.0 g (3.4×10^{-3} mol) of **1** was added 4.6 g (0.016 mol) of PBr_3. The solution was stirred magnetically while being heated gently by means of an oil bath. When the temperature of the bath approached 100°, the dihydroxy compound was completely dissolved in the PBr_3. At 115° a very obvious exothermic reaction took place with the formation of an orange solid. The oil bath was removed and the reaction mixture was allowed to cool to room temperature. The excess PBr_3 was hydrolyzed cautiously with water. Excess water was added and the reaction was stirred at room temperature for 1 hr. The orange solid was collected by filtration and then added slowly, with stirring, to a solution of concentrated ammonium hydroxide. After complete reaction, a light brown solid formed. Recrystallization from ethyl acetate–methanol gave 2.4 g (35%) of a white, cubic solid: mp 132–134°; uv max (95% EtOH) 252 nm (ϵ 27,000) and 246 (23,000); ir (Nujol) 1600, 1280, 1215, 950, 745, 685, 650, 510 cm^{-1} (w); nmr ($CDCl_3$) δ 7.2 (m, 4), 6.8 (m, 6), 4.1–3.8 (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 422 (19), 343 (M − Br) (94), 329 (M − CH_2Br) (4), 250 (33), 158 (50), 145 (100), 132 (74), 104 (70), 91 (28), 77 (57).

Anal. Calcd for $C_{18}H_{20}N_2Br_2$: C, 50.97; H, 4.75. Found: C, 50.89; H, 4.97.

Isolation of *cis*-2,5-Bis(bromomethyl)-1,4-diphenylpiperazine (**5**).—The ethyl acetate–methanol mother liquor from the recrystallization of **4** in the previous preparation was evaporated. This gave a white powder, which after repeated recrystallizations from ethyl acetate–methanol yielded white, needle-like crystals:

(5) Kindly supplied by Professor G. G. Gallo, Lepetit Spa, Milano, Italy.

(6) Kindly supplied by Merck Sharp and Dohme Co., through arrangements with Dr. Norman Brink.

(7) V. R. Gaertner, private communication.

(8) J. B. McKelvey, B. C. Webre, and R. R. Benerito, *J. Org. Chem.*, **25**, 1424 (1960).

mp 117–119°; ir (Nujol) 1600, 1280, 1245, 1215, 945, 745, 685, 655, 520 cm^{-1} (m); nmr ($CDCl_3$) δ 7.3 (m, 4), 6.9 (m, 6) 4.2–2.8 (m, 10). The mass spectrum and the ultraviolet spectrum were identical with those of 4. Through many attempts, the maximum yield obtainable for this isomer was 12%.

Anal. Calcd for $C_{18}H_{20}N_2Br_2$: C, 50.97; H, 4.75. Found: C, 51.12; H, 4.78.

Preparation of *cis*-2,6-Bis(bromomethyl)-1,4-diphenylpiperazine Monohydrobromide (3).—This procedure was similar to that for the preparation of 4. After reaction of 1 with PBr_3 and prior to neutralization with concentrated ammonium hydroxide, the orange solid was recrystallized from ethyl acetate–methanol. Several recrystallizations yielded a white, crystalline compound: mp 217–220° dec; ir (Nujol) 2290, 2200, 1600, 1260, 1225, 950, 745, 700, 685, 645 cm^{-1}; nmr (CF_3COOH) δ 7.9 (m, 10), 5.4 (m, 2), 4.2–4.3 (m, 4), 2.4 (d, 4). This material was only slightly soluble in water, but gave a positive test for ionic halogen using silver nitrate reagent.

Anal. Calcd for $C_{18}H_{21}N_2Br_3$: C, 42.80; H, 4.19. Found: C, 43.15; H, 4.22.

Reaction of 4 with Anhydrous Hydrogen Bromide.—To 100 ml of ether–cyclohexane (8:2) was added 1 g of 4 and the solution was heated gently to dissolve all the material. Through this solution was passed a stream of anhydrous hydrogen bromide and after 5 min the solution became cloudy. The gas was passed through the solution for an additional 10 min. The solution was evaporated *in vacuo* and yielded a white solid, mp 160–180°. This solid was extracted with two 20-ml portions of chloroform, and most of the material was dissolved. The remaining insoluble material, 0.2 g, had mp 219–220°. The infrared spectrum of the solid melting at 219–220° was identical with that of 3.

Reaction of 4 with Lithium Aluminum Hydride ($LiAlH_4$) to 6.—To 1.5 g (0.0035 mol) of 4 in 10 ml of dry tetrahydrofuran (THF) was added a solution of 1 g of $LiAlH_4$ in 20 ml of dry THF, and the solution was stirred at room temperature for 5.5 hr. Excess $LiAlH_4$ was hydrolyzed with ethyl acetate, and, after the reaction ceased, 15 ml of water was added. After the reaction mixture was stirred overnight, a white solid appeared. To this was added excess water, and the solution was filtered. The lithium salts were washed well with water and ether. The ether layer was separated, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to a volume of 3 ml. Vpc analysis of the residue showed the presence of four species, and the major product appeared to be present to the extent of 90%. This was trapped from column B, using a column temperature of 200° and a flow rate of helium of 120 ml/min: ir (Nujol) 3020, 2950, 2780, 1600, 1500, 1450, 1370, 1340, 1300, 1240, 1150, 1100, 1030, 1000, 930, 890, 810, 770, 745, 690 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 266 (42), 251 (27), 146 (63), 132 (18), 119 (47), 105 (100), 104 (67); nmr ($CDCl_3$) δ 7.2 (m, 10), 3.5 (q, 2), 3.3 (m, 2), 2.7 (q, 2), 0.86 (d, 6).

Reaction of 5 with $LiAlH_4$ to 7.—A 1-g sample of 5 was dissolved in 10 ml of THF and the solution was added to a solution of 0.5 g of $LiAlH_4$ in 15 ml of THF. The remainder of the procedure was identical with that described for the reaction of 4 with $LiAlH_4$. The major product was isolated by vpc trapping techniques from column B, using a column temperature of 200° and a flow rate of 120 ml/min. The mass spectra showed a molecular ion at *m/e* 266 and was essentially identical with that of product isolated from the reaction of 4 with $LiAlH_4$: ir (Nujol) 3070, 3020, 2980, 2830, 1600, 1500, 1450, 1380, 1250, 1160, 1060, 1030, 990, 910, 865, 840, 785, 745, 685, 550, 510 cm^{-1}; nmr ($CDCl_3$) δ 7.2 (m, 4), 6.8 (m, 6), 3.5 (m, 2), 3.5 (q, 2), 2.9 (q, 2), 1.13 (d, 6).

Isolation of 2,5-Diphenyl-2,5-diazabicyclo[2.2.2]octane (8).—The last peaks observable on the gas chromatograms of the two foregoing reactions were trapped. The mass spectrum gave a molecular ion at *m/e* 264 and no M − 15 fragment; uv max (95% EtOH) 252 nm (ε 27,000); ir (Nujol) 3060, 3040, 3030, 2960, 2900, 2840, 1600, 1500, 1455, 1370, 1340, 1320, 1300, 1245, 1220, 1190, 1160, 1125, 1080, 1055, 1030, 990, 950, 905, 870, 795, 750, 690, 540, 520, 490 cm^{-1}; nmr ($CDCl_3$) δ 7.2 (m, 4), 6.8 (m, 6), 4.34 (m, 2) 3.26 (m, 4), 2.00 (m, 4).

Reaction of 4 with Lithium Aluminum Deuteride.—The procedure used here was identical with the one described for the reaction of 4 with $LiAlH_4$ except that reduction was carried out with $LiAlD_4$. Analysis and isolation of the products was carried out by vpc using column B, a column temperature of 200°, and a flow rate of 120 ml/min. The mass spectrum of the major product gave a molecular ion at *m/e* 268 with a major fragment at M − 16 ($-CH_2D$); nmr ($CDCl_3$) δ 7.4–6.8 (m, 10), 3.5 (q, 2), 3.25 (m, 2), 2.75 (q, 2), 0.88 (t, 2), 0.82 (t, 2).

Preparation of *cis*-2,6-Dimethyl-1,4-diphenylpiperazine (6).—The procedure used was a modification of the one used by Starker[9] for the preparation of monophenylpiperazines. A solution containing 12 g (0.10 mol) of *cis*-2,6-dimethylpiperazine (Aldrich) in 24 ml (0.20 mol) of bromobenzene and 65 ml of THF was added to a solution of 100 ml (0.20 mol) of phenyllithium in ether (Alpha Inorganics). The addition was carried out with stirring and at such a rate that the temperature did not exceed 70°. After total addition (3 hr), the reaction was allowed to come to room temperature. The excess phenyllithium was hydrolyzed with water (caution—the hydrolysis reaction had a latent period). The organic layer was separated and was evaporated under reduced pressure. Vpc analysis, using column A, a temperature of 185°, and a flow rate of 60 ml/min, gave a peak identical in retention time with the product isolated from the reaction of 4 with $LiAlH_4$. Many peaks appeared on the chromatogram, and the desired product was estimated to be present to the extent of about 2%. This dark brown, oily residue (10 ml) was extracted with 30 ml of 6 *N* hydrochloric acid, and the aqueous solution was extracted with ether repeatedly until no more biphenyl was observed in the ether extract (by vpc analysis). The acidic aqueous solution was neutralized with approximately 29% aqueous ammonium hydroxide until the solution became basic to litmus. The resulting free base was extracted with ether, and the ether layer was separated, dried over magnesium sulfate, and evaporated *in vacuo* to give a dark brown oil. The desired compound was trapped by techniques using column B at a column temperature of 215° and a flow rate of 180 ml/min. The nmr spectrum in $CDCl_3$ was identical with that of the product of the reaction of 4 with $LiAlH_4$.

Preparation of *cis*-2,5-Dimethyl-1,4-diphenylpiperazine (7).—The quantities and conditions were similar to those described for the preparation of 6 except that after addition of the starting materials to the phenyllithium, the reaction was heated and stirred at 41° overnight and then hydrolyzed with water. The yield of the compound did not appear to increase under these conditions (2% by glc analysis). The infrared and nmr spectra were identical with those of the product of the reaction of 5 with $LiAlH_4$.

Reaction of 4 with Magnesium.—In 5 ml of dry THF was placed 0.5 g of magnesium turnings and a small crystal of iodine to initiate the reaction. To this was added 5 ml of a solution containing 1 g of 4 in 25 ml of THF. No apparent reaction took place. A small amount of *n*-butyl bromide was added and the reaction was brought to reflux. The remainder of the solution of 4 was then added, and the reaction mixture seemed to darken. After the system was maintained at reflux for 5 hr the solution was black. The reaction was allowed to cool to room temperature and 5 ml of ethanol was added to decompose the Grignard reagent. After the ethanol reaction had ceased, 10 ml of water was added and the reaction mixture was stirred overnight. More water was added to give a two-phase system with ether, and the reaction mixture was extracted with two 40-ml portions of ether. The extracts were combined, dried over magnesium sulfate, and evaporated *in vacuo*. Vpc analysis using column B, a column temperature of 215°, and a flow rate of 180 ml/min gave a peak of retention time 39 min. This peak was trapped and showed identical vpc retention time and infrared and nmr spectra with those of the sample of 8, which was isolated from the reaction of 4 with $LiAlH_4$. As estimated by vpc, the product was obtained in 80% yield.

Reaction of 4 with Methyllithium.—To a solution of 4.0 ml of 2.6 *M* methyllithium (Alpha Inorganics) in 25 ml of ether was added a solution containing 1.0 g (0.0024 mol) of 4 in 25 ml of THF. The reaction was brought to reflux and was maintained at these conditions for 20 hr. The reaction mixture gave a yellow solution and a white precipitate. When water was added to hydrolyze the excess methyllithium, the white precipitate dissolved, giving a two-layer system. The ether layer was separated and the aqueous layer was extracted repeatedly with ether. The ether layers were combined, dried over magnesium sulfate, and evaporated *in vacuo*. Vpc analysis, using column B, a column temperature of 255°, and a flow rate of 180 ml/min, showed one major product and five smaller peaks. The major product was trapped and proved to be identical in all spectral properties with the sample of 8 which was isolated from the re-

(9) L. N. Starker, J. K. Paul, and L. Goldman, U. S. Patent 3,173,917 (Cl. 260–268); *cf. Chem. Abstr.*, **62**, 13160*d* (1965).

action of 4 with $LiAlH_4$. It was estimated by vpc to be present to the extent of 50% of the reaction mixture.

The Nmr Spectrum of 2,5-Diazabicyclo[2.2.2]octane (13).—2,5-Diazabicyclo[2.2.2]octane dihydrochloride was obtained from Merck.[6] This sample was dissolved in D_2O and the nmr spectrum showed the following signals: δ 2.20 (4 H, m, 80-Hz width), 3.69 (4 H, octet), and 4.05 (2 H, m). To this sample was added concentrated ammonium hydroxide such that the solution was just basic to litmus. The nmr spectrum of this sample had the following signals: δ 2.25 (4 H, m, 80 Hz width) and 3.53 (6 H, m). In the dihydrochloride salt the signal at δ 3.69 represented an AB portion of an ABX system where J_{AX} = 2.3, J_{BX} and J_{AB} = 11 Hz.

The Nmr Spectrum of 3,8-Dibenzyl-3,8-diazabicyclo[3.2.1]-octane (12).—The sample used here was supplied by Gallo,[5] who prepared the sample by a procedure described by Blackman.[10] The nmr of this sample had the following signals: δ 7.25 (10 H, m), 3.45 (4 H, d), 3.0 (2 H, m), 2.35 (4 H, octet), 1.85 (4 H, m). The signal at δ 2.35 represented the AB portion of an ABX pattern in which J_{AX} = 3, J_{BX} = 2, and J_{AB} = 10 Hz.

Conversion of 4 to 5.—A 1-g sample of 4 was placed in a vacuum sublimator and was heated gradually from 50 to 170° over a 3-hr period at 4 mm. No visual sublimation occurred. The resulting material appeared as a slightly darkened melt. This was taken up in methanol–ethyl acetate. A minimum amount was used such that only the dark impurities dissolved. The remaining white, crystalline solid was recrystallized from ethanol–ethyl acetate to give a solid, mp 117–119°, whose infrared and nmr spectra were identical with those of a sample of 5. The above conversion also occurred on recrystallization. A 1-g sample of 4 was recrystallized from ethanol–ethyl acetate to give 0.80 g of pure material. Evaporation of the mother liquor gave 0.15 g of a material whose melting point and nmr spectrum were identical with those of a sample of 5.

Registry No.—**1**, 30715-42-5; **3**, 30715-43-6; **4**, 30788-18-2; **5**, 30715-44-7; **6**, 30715-45-8; **7**, 24425-88-5; **8**, 30715-47-0; **12**, 17740-42-0; **13**, 658-24-2.

(10) S. W. Blackman and R. Blatzly, *J. Org. Chem.*, **26**, 2750 (1961).

1,1-Dimethyl-1-sila-2,3:6,7-dibenzocycloheptatriene. A Dibenzosilepin

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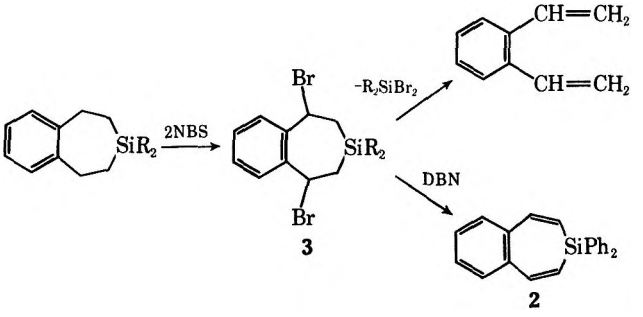
The first example of the dibenzosilepin ring system has been synthesized. 1,1-Dimethyl-1-sila-2,3:6,7-dibenzocycloheptatriene (6) was prepared through cyclization of *o,o'*-dilithiobibenzyl and dichlorodimethylsilane followed by free-radical (NBS) dibromination and finally debromination with metallic zinc. The nonplanarity of 6 could not be established through low-temperature nmr studies. The uv spectrum of 6 revealed no evidence of ($\pi \rightarrow$ d) π bonding.

When the vast research effort which has been exerted toward the synthesis and study of heterocycloheptatrienes [*e.g.*, oxepines (**1a**), azepines (**1b**), thiepins (**1c**), and diazepines][2] is considered, it is rather surprising to note that only one proven[3] and two possible[4,5] examples of a silicon-containing cycloheptatriene (silacycloheptatriene or silepin, **1d**) have been reported. This dearth

1a, X = O
b, X = NR
c, X = S
d, X = SiR_2

of information in the chemical body of knowledge is particularly glaring in view of the unique situation for the possible observation of ($\pi \rightarrow$ d) π bonding[6] in the silepin ring system. It could be hoped that the aromatic character derived from cyclic delocalization of the six π electrons would put this type of valence expansion to a stern test.

A search of the literature revealed a single unambiguous example of an intentional silepin synthesis, the benzosilepin **2**, which originally failed[7] due to the extreme lability of the synthetic intermediate, 1,5-dibromo-3,3-dimethyl-1,2,4,5-tetrahydro-3*H*-3-benzosilepin (**3**), which was due to operation of that persistent



stumbling block of organosilicon chemistry, the β effect.[8] Birkofer[3] was finally able to prepare **2**, in low yield, through the use of 1,5-diazabicyclo[4.3.0]nonene (DBN) as a dehydrobromination agent. Examination of the carbon–carbon double bond stretching frequencies in the infrared spectrum of **2** led Birkofer to conclude that there was interaction between the π electrons of the olefinic system and the vacant d orbitals of silicon. However, it should be noted that these ir bands (1592 and 1550 cm^{-1}) were not significantly different from the double-bond stretches of other vinylsilanes (*e.g.*,

(1) National Science Foundation Undergraduate Research Participant, summers of 1969 and 1970.

(2) For an excellent review of the syntheses and chemistry of azepines, oxepines, and thiepins, see L. A. Paquette in "Nonbenzenoid Aromatics," Vol. I, J. P. Snyder, Ed., Academic Press, New York, N. Y., 1970, pp 249–310.

(3) L. Birkofer and H. Haddad, *Chem. Ber.*, **102**, 432 (1969).

(4) H. Gilman, S. G. Cottis, and W. H. Atwell, *J. Amer. Chem. Soc.*, **86**, 5584 (1964).

(5) K. A. Andrianov, L. M. Vokova, N. V. Delazari, and N. A. Chumaevskii, *Akad. Nauk Latv. SSR*, 435 (1967), report that dimethylmethoxychlorosilane and *o*-dichlorobenzene react with sodium to afford 1,1-dimethyltribenzosilepin in <0.02% yield.

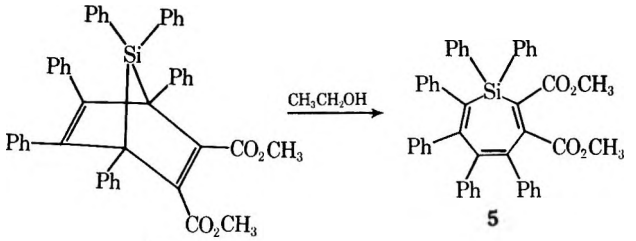
(6) For a summary of the evidence relating to (p → d) π and ($\pi \rightarrow$ d) π bonding to silicon, see E. A. V. Ebsworth in "Organometallic Compounds of the Group IV Elements," Vol. 1, A. G. MacDiarmid, Ed., Marcel Dekker, New York, N. Y., 1968, part 1, Chapter 1.

(7) L. Birkofer and E. Kramer, *Chem. Ber.*, **102**, 427 (1969).

(8) C. Eaborn, "Organosilicon Compounds," Butterworths, London, 1960.

cis-β-trimethylsilylstyrene, 1590 and 1570 cm^{-1})[9] which do *not* have the possibility for cyclic conjugation that is present in the silepin ring system. The nmr of **2** was quite similar to that of the analogous benzostannepin,[10] but quite different from that of the tropylium analog, 3-phenyl-3-benzoborepin[11] (*e.g.*, =SiCH=C, δ 6.28, for **2** *vs.* -BCH=C, δ 7.72).

Gilman[4] has tentatively suggested structure **5** for the product from decomposition of the 7-silanorbornadiene (**4**) in ethanol. Obviously the extensive ring substitution of **5** makes structural assignment a virtually impossible task without the use of X-ray diffraction techniques.



4 **5**

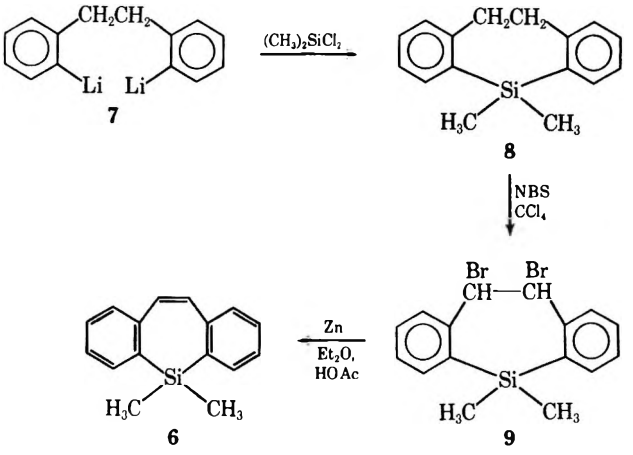
We now report the synthesis of the first dibenzosilepin derivative, 1,1-dimethyl-1-sila-2,3:6,7-dibenzocycloheptatriene (**6**).[12]

The most obvious route into the dibenzosilepin ring system is through cyclization of *o,o'*-dilithiobibenzyl (**7**)[13] and some dihalosilane, followed by introduction of the final double bond. Indeed a dihydrodibenzosilepin has been reported by Gilman from this very route when dichlorodiphenylsilane was employed.[14]

Addition of a solution of dichlorodimethylsilane in ether to an equimolar solution of *o,o'*-dilithiobibenzyl under nitrogen at room temperature afforded, upon work-up, 1,1-dimethyl-1-sila-2,3:6,7-dibenzocycloheptadiene (**8**) as a colorless liquid in 56% yield. Dihydrosilepin **8** analyzed correctly upon combustion analysis and exhibited a strong parent ion at *m/e* 238 in its mass spectrum. The nmr spectrum was consistent with this structure: $\delta_{TMS}^{CCl_4}$ 0.50 (s, 6 H, =Si-Me_2), 3.13 (s, 4 H, $-CH_2CH_2-$), 6.82–7.68 (m, 8 H, Ar).

In our hands bromination of **8** with NBS at 50° allowed isolation of 1,1-dimethyl-1-sila-2,3:6,7-dibenzo-4,5-dibromocycloheptadiene (**9**) in *ca.* 30% yield.

Dibromide **9** was converted into the title compound (**6**) through treatment with zinc metal in refluxing ether. Dibenzosilepin (**6**) was obtained in 82% yield as a colorless, viscous liquid. The nmr spectrum consisted of a singlet of area 6 at δ 0.46 (=$SiMe_2$), a singlet of area 2 at δ 6.88 (-CH=CN-), and a multiplet of area 8 centered at δ 7.41 (aromatic). The conversion of **8** to **6** was performed by Corey[12] through monobromination (NBS) and dehydrohalogenation (potassium acetate or DBN) while Cartledge[12] reports dehydrogenation of **8** with DDQ.



It is of considerable interest to determine the effects of introduction of a silicon atom into this well-examined ring system. A number of 2,3:6,7-dibenzo derivatives of seven-membered cyclic conjugated systems (thiepin, azepin, oxepin, tropilidene, tropone, and heptafulvene)[15] have been examined by physical and chemical means. In each case these molecules were found to be nonplanar. Certainly the dibenzosilepin is not the ideal silepin in which to search for cyclic ($\pi \rightarrow$ d) π delocalization in view of the markedly decreased stability of the 1,2:5,6-dibenzotropylium cation in comparison to the parent tropylium cation.[16]

The room temperature nmr spectrum of **6** reveals the $SiCH_3$ groups as a clean singlet which can arise either from a rapidly inverting boat form or a planar system. In a low-temperature nmr study, the $Si(CH_3)_2$ resonance remains a sharp singlet until *ca.* −80°. Slight broadening commences at this temperature, but, since olefinic and aromatic signals also begin to broaden, this effect must be ascribed to increased viscosity. It is therefore not possible to state whether **6** is inverting or planar, although the latter situation is considered highly unlikely. Work is presently in progress to resolve that question through X-ray crystallography.

The most telling evidence against any significant cyclic delocalization *via* ($\pi \rightarrow$ d) π bonding comes from the uv spectrum of **6**. Dihydrosilepin **8** exhibits a uv spectrum [λ_{max}^{EtOH} 278 mμ (log ε 2.65), 271 (2.70), 265 infl (2.58)] which is extremely similar to that of the all-carbon analog, 1,2:4,5-dibenzocycloheptadiene [λ_{max}^{EtOH} 274 mμ (log ε 2.84), 271 (2.91), 265 (2.94)][17] while **6** possesses a simple spectrum [λ_{max}^{EtOH} 294 mμ (log ε 4.1)] which does not exhibit a bathochromic shift of a magnitude required to postulate any significant involvement of silicon d orbitals in cyclic conjugation. This conclusion becomes evident upon examination of the uv spectrum of several pertinent model compounds:[18] dibenzo[*a,e*]cycloheptatriene [λ_{max}^{EtOH} 288 mμ (log ε 4.19)],[19] dibenzo[*b,f*]thiepin [λ_{max}^{EtOH} 295 mμ (log ε

(9) D. Seyferth, L. G. Vaughan, and R. Suziki, *J. Organometal. Chem.*, **1**, 437 (1964).

(10) A. J. Leusink, J. G. Noltes, H. A. Budding, and G. J. M. van der Kerk, *Recl. Trav. Chim. Pays-Bas*, **83**, 1036 (1964).

(11) A. J. Leusink, W. Drenth, J. G. Noltes, and G. J. M. van der Kerk, *Tetrahedron Lett.*, 1263 (1967).

(12) After our work was complete and the manuscript submitted, there appeared two reports of the synthesis of **8** and **6**: J. Y. Corey, M. Dueber, and B. Bichlmeir, *J. Organometal. Chem.*, 167 (1971), and F. K. Cartledge and P. D. Mollere, *ibid.*, 175 (1971). The three reports agree with regard to the conclusions about electronic delocalization in the central ring and physical constants. The sole exception is the nmr spectrum of **8** reported by Corey, which is somewhat at odds with that found by Cartledge and this report.

(13) R. L. Letsinger and I. H. Skoog, *J. Amer. Chem. Soc.*, **77**, 5176 (1955).

(14) H. Gilman and W. H. Atwell, *J. Org. Chem.*, **28**, 2906 (1963).

(15) M. Nógrádi, W. D. Ollis, and I. O. Sutherland, *Chem. Commun.*, 158 (1970), and references cited therein.

(16) G. Berti and A. DaSettimo, *Ann. Chim. (Rome)*, **49**, 1237 (1959).

(17) C. D. Gutsche and H. E. Johnson, *J. Amer. Chem. Soc.*, **77**, 5933 (1955).

(18) Unfortunately, the interesting comparison with the uv spectrum of **2** cannot be made as this spectrum was not reported in ref 3.

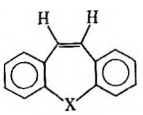
(19) E. D. Bergmann and M. Rabinovitz, *J. Org. Chem.*, **25**, 827 (1960).

3.70), 262 (4.47)],[19] *cis*-stilbene [λ_{max}^{EtOH} 280 mμ (log ε 4.02)],[20] 1,2:4,5-dibenzotropylium cation [λ_{max} 540 mμ (log ε 3.51), 508 (3.51), 397 (3.94), etc.][21] However, the nagging problem of separation of the inductive effect of the heteroatom from d-orbital stabilization of the π* orbitals, *i.e.*, that we are observing the results of two counteracting effects (see ref 5, pp 29–35), continues to plague this type of analysis.

A cursory inspection of the chemical shift of the two olefinic protons would appear to indicate some polarization of **6**, if not actual cyclic delocalization. With one exception the comparisons which can be made from Table I indicate a separation of charge in **6** in the direction which would be expected from (π → d) π bonding. However, without specific knowledge of the effects of the various functional group anisotropies in Table I any conclusions with regard to polarization of **6** must be regarded as tentative, especially in view of the reported position (418 Hz) for the corresponding hydrogens in dibenzo[*a*,*e*]cycloheptatriene.[23]

Table I

Chemical Shift Positions of Olefinic Protons



cis-Stilbene (393 Hz)[a]

X = C=CH$_2$ (402 Hz)[a]
X = C=O (414.5 Hz)[a]
X = C=C(CN)$_2$ (421 Hz)[a]
X = CHCH$_2$OH (390 Hz)[a]
X = CH$_2$ (418 Hz)[b]

6 (413 Hz)[c]

[a] M. Rabinovitz, I. Agranat, and E. D. Bergmann, *Tetrahedron*, **22**, 225 (1966). [b] E. Müller and H. Kessler, *Justus Liebigs Ann. Chem.*, **692**, 58 (1966). [c] This work.

The mass spectrum of **6** (70 eV) is relatively uneventful, revealing a strong parent ion (*m*/*e* 236) and a facile loss of ·CH$_3$ (*m*/*e* 221, M* 206.6). The intensity of this fragment ion (*m*/*e* 221) is close to that of the parent ion and insufficient to postulate any unusual stability for the silatropylium cation.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Routine proton nmr spectra were determined on a Varian A-60 instrument employing tetramethylsilane as the internal standard. Low-temperature nmr spectra were measured on a Perkin-Elmer R20-B instrument. Uv spectra were recorded on a Cary Model 14 spectrophotometer. Analyses were carried out by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany.

o,*o*′-**Dilithiobibenzyl** (7).—This material was prepared by the method of Letsinger and Skogg.[13] A solution consisting of 80 ml (1.6 *M* in hexane) of *n*-butyllithium and 150 ml of anhydrous ether was slowly added under argon to a stirred solution of 20 g (59 mmol) of *o*,*o*′-dibromobibenzyl in 300 ml of ether kept at 5°. After completion of addition, the reaction mixture was refluxed for 1 hr.

1,1-Dimethyl-1-sila-2,3:6,7-dibenzocyclohepta-2,6-diene (**8**).—A solution of 7.7 g (60 mmol) of dry dimethyldichlorosilane in 200 ml of anhydrous ether was slowly added under argon to the uncooled solution described above. The reaction mixture was allowed to stir for an additional 3 hr and then hydrolyzed with 1 *N* HCl. The ether layer was separated, washed with water, and dried over magnesium sulfate. Evaporation of the ether *in vacuo* afforded a yellow oil which upon distillation yielded 7.9 g (56%) of colorless **8**. Analytically pure **8** was obtained by careful distillation on a Nester–Faust annular Teflon spinning-band column: bp 112° (0.1 mm); ν_{max}^{neat} 2930, 1590, 1480, 1400, 1265, 1255, 1138, 1117, 1074 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 0.50 (s, 6 H), 3.13 (s, 4 H), 6.82–7.68 (m, 8 H); mass spectrum *m*/*e* 238 (parent ion).

Anal. Calcd for C$_{16}$H$_{18}$Si: C, 80.61; H, 7.61; Si, 11.83. Found: C, 80.57; H, 7.47; Si, 11.76.

1,1-Dimethyl-1-sila-2,3:6,7-dibenzo-4,5-dibromocyclohepta-2,6-diene (**9**).—To a stirred solution of **7** (18.0 g, 75.5 mmol) and a catalytic amount of benzoyl peroxide in carbon tetrachloride (1 l.) under a nitrogen atmosphere at 50° was added *N*-bromosuccinimide (27.0 g, 152 mmol). The reaction mixture was allowed to stir at 50° overnight and cooled, and the succinimide was removed by filtration. Evaporation of solvent, percolation through a silica gel column (hexane), and recrystallization from methanol afforded white, crystalline **9**: yield 9.0 g (30%); mp 178.0–178.5°; ν_{max}^{KBr} 2930, 1420, 1385, 1287, 1251, 1241, 1229, 1148, 1128, 1084, 1073 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 0.53 (s, 6 H), 5.68 (s, 2 H), 7.25 (m, 8 H).

Anal. Calcd for C$_{16}$H$_{16}$Br$_2$Si: C, 48.50; H, 4.07. Found: C, 48.56; H, 4.05.

1,1-Dimethyl-1-sila-2,3:6,7-dibenzocycloheptatriene (**6**).—A solution of dibromide **9** (10.0 g, 25 mmol) in ether (250 ml) was added, at a rate sufficient to maintain gentle refluxing, to a stirred mixture of activated zinc (2 g), ether (500 ml), and a few drops of acetic acid. After addition was completed the mixture was stirred for 2 hr, filtered, and washed with water. Removal of solvent *in vacuo* afforded a light yellow oil which was distilled to yield colorless **6**: 5.0 g (82%); bp 116.5–117.5° (0.2 mm); mass spectrum *m*/*e* 236; $\delta_{TMS}^{CCl_4}$ 0.46 (s, 6 H), 6.88 (s, 2 H), 7.41 (m, 8 H).

Anal. Calcd for C$_{16}$H$_{16}$Si: C, 81.29; H, 6.82; Si, 11.88. Found: C, 81.26; H, 6.73; Si, 11.83.

Registry No.—**6**, 29668-89-1; **8**, 29784-73-4; **9**, 29668-90-4.

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(20) R. N. Beale and E. M. F. Roe, *J. Chem. Soc.*, 2755 (1953).
(21) G. Naville, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **43**, 1225 (1960).

Mesoionic Compounds. XIV. Mesoionic Compounds of the Imidazole Series[1]

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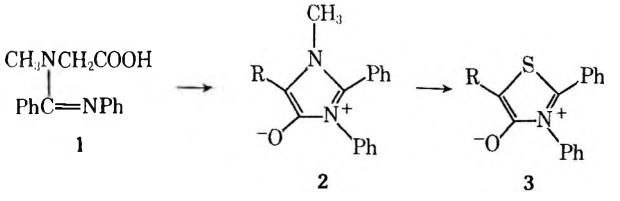
Reaction of *N*-methyl-*N*-(*N'*-phenylbenzimidoyl)aminoacetonitrile with dry HCl gave 4-amino-2,3-diphenyl-1-methylimidazolium chloride which, with acetic anhydride, followed by sodium bicarbonate, formed *anhydro*-4-acetimino-2,3-diphenyl-1-methylimidazolium hydroxide. This was also obtained from the reaction of acetyl chloride–benzene, followed by sodium bicarbonate, with the nitrile. An analogous series of 4-benzoylimino derivatives was also prepared. With warm, dilute potassium hydroxide solution, the nitrile gave 4-anilino-1-methyl-2-phenylimidazole which was also obtained from 4-amino-2,3-diphenyl-1-methylimidazolium chloride, through a Dimroth-type rearrangement. These exocyclic imino compounds showed very ready 1,3-dipolar reactivity with acetylenic and azo type dipolarophiles. With dimethyl acetylenedicarboxylate, the corresponding pyrrole was formed with possible extrusion of *N*-benzoyl-*N'*-phenylcarbodiimide from the initial cycloadduct.

Mesoionic derivatives of the imidazole ring system were first described[2] in 1959, though several ring-fused compounds containing the imidazole nucleus and now represented as mesoionic compounds were prepared earlier.[2,3] The monocyclic system, represented by *anhydro*-4-hydroxy-2,3-diphenyl-1-methylimidazolium hydroxide was prepared in the form of its 5-acetyl and 5-propionyl derivative (**2**, R = $COCH_3$ and COC_2H_5, respectively) by cyclization of *N*-(*N'*-phenylbenzimidoyl)glycine (**1**) with the appropriate acid anhydride. The action of acid or base had no effect on **2**, and it was remarkably stable in comparison with other mesoionic compounds. Representatives of this mesoionic ring system with an exocyclic sulfur atom are known and have been prepared from other mesoionic systems and phenyl isothiocyanate. Thus, *anhydro*-4-mercapto-1-methyl-2,3,5-triphenylimidazolium hydroxide was obtained[4] from anhydro-2,4-diphenyl-5-hydroxy-3-methyloxazolium hydroxide and phenyl isothiocyanate in xylene at 70°. Under similar conditions *anhydro*-2-aryl-5-hydroxy-3-methylthiazolium hydroxides also gave the corresponding *anhydro*-2-aryl-4-mercapto-1-methyl-3-phenylimidazolium hydroxides.[5]



Our studies in other mesoionic ring systems suggested that a study of the imidazole system would be of interest. Experience with other five-membered mesoionic systems indicated that the stability of **2** was due to the 5-acyl group which could quite effectively delocalize the exocyclic negative charge on the oxygen atom. We had found previously that, though *anhydro*-2,3-diphenyl-4-hydroxythiazolium hydroxide (**3**, R = H) was an extremely active substrate for nucleophiles and dipolarophiles, its 5-acyl derivative (**3**, R = $COCH_3$) was quite stable.[6] Thus the behavior of *anhydro*-4-hydroxy-2,3-diphenyl-1-methylimidazolium hydroxide (**2**, R = H) with acetylenic and olefinic dipolarophiles was of particular interest.

The most direct route to **2** (R = H) would be the acetic anhydride–triethylamine cyclization of *N*-(*N'*-phenylbenzimidoyl)glycine (**1**), analogous to the procedure used successfully for the synthesis of **3** (R = H). Attempts to prepare the acid **1** by condensation of sarcosine (or its ester) with *N*-phenylbenzimidoyl chloride were unsuccessful. An alternative route, the hydrolysis of *N*-methyl-*N*-(*N'*-phenylbenzimidoyl)-aminoacetonitrile (**4**), was employed in the original synthesis of **2** (R = $COCH_3$) and has recently been investigated by other workers with no success.[7] We have also found that the hydrolysis of **4** with 2% aqueous HCl[2] did not yield the acid **1** but gave *N*-methyl-*N*-(*N'*-phenylbenzimidoyl)acetamide hydrochloride (**5**), contaminated with benzanilide and sarcosine hydrochloride. Variations of these hydrolysis conditions did not appreciably alter the above results. However, when 20% HCl was used, the hydrochloride of the desired acid was obtained in small amounts in an impure state. This was converted into the sodium salt[2] which, with triethylamine (or pyridine) and acetic anhydride under a wide variety of conditions, always gave the acetyl derivative **2** (R = $COCH_3$). These results indicate that the unsubstituted mesoionic system **2** (R = H) is extremely susceptible to electrophilic attack and suggest a high-electron density at the 5 position of the nucleus. Recent MO calculations[7] show a considerably larger degree of negative charge associated with the C_4-C_5 atoms in **2** (R = H) compared with that in the sydnones.[8] The extremly facile acetylation is understandable in these terms. These calculations indicate, moreover, that mesoionic imidazoles should show considerable 1,3-dipolar reactivity though we found that the 5-acetyl compound (**2**, R = $COCH_3$) was completely unresponsive to a variety of dipolarophiles and heterocumulenes.

The best known[9] examples of mesoionic compounds with a negatively charged exocyclic nitrogen atom, either in the protonated form or with the negative charge delocalized to some extent over an acyl group

(1) (a) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged. (b) Part of this work has appeared in a preliminary communication: K. T. Potts, S. Husain, and S. Husain, *Chem. Commun.*, 1360 (1970).

(2) A. Lawson and D. H. Miles, *J. Chem. Soc.*, 2865 (1959).

(3) E. Besthorn and J. Ibel, *Ber.*, **37**, 1236 (1904); F. Knollpfieffer and K. Schneider, *Justus Leibigs Ann. Chem.*, **530**, 34 (1937); D. L. Hammick and A. M. Roe, *Chem. Ind. (London)*, 900 (1953).

(4) R. Huisgen, E. Funke, F. C. Schaefer, H. Gotthardt, and E. Brunn, *Tetrahedron Lett.*, 1809 (1967).

(5) K. T. Potts and D. N. Roy, *Chem. Commun.*, 1062 (1968).

(6) K. T. Potts, U. P. Singh, and E. Houghton, *ibid.*, 1128 (1969).

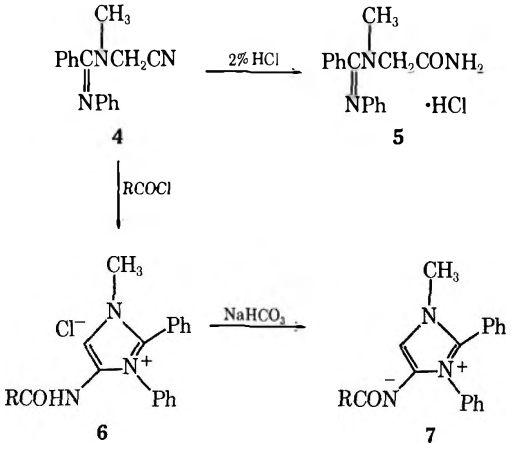
(7) E. B. Roche and D. W. Stansloski, *J. Heterocycl. Chem.*, **7**, 139 (1970).

(8) L. B. Kier, *J. Pharm. Sci.*, **55**, 807 (1966); E. B. Roche and L. B. Kier, *Tetrahedron*, **24**, 1673 (1968).

(9) H. Chosho, K. Ichimura, and M. Ohta, *Bull. Chem. Soc. Jap.*, **37**, 1670 (1964); M. Ohta and M. Sugiyama, *ibid.*, **38**, 598 (1965).

attached to the nitrogen atom, are the sydnone imines.[10] It was of importance, then, to prepare the corresponding imino derivatives of the imidazole system **7**, and the nitrile **4** was a suitable starting point for this synthesis.

Reaction of **4** with benzoyl chloride in dry benzene readily gave 4-*N*-benzamido-2,3-diphenyl-1-methylimidazolium chloride (**6**, R = Ph) which, when treated

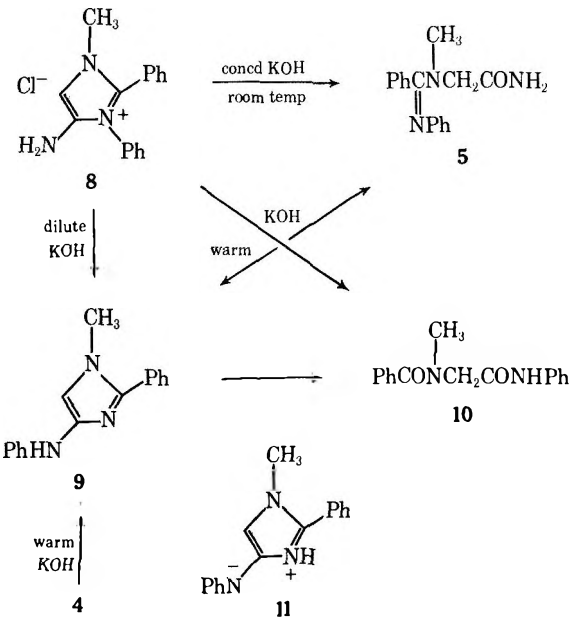


with aqueous sodium bicarbonate, formed *anhydro*-4-*N*-benzoylimino-2,3-diphenyl-1-methylimidazolium hydroxide (**7**, R = Ph). Analytical and spectral data, especially a carbonyl absorption at 1580 cm^{-1}, and a singlet proton resonance at τ 2.37 in the corresponding *N*-acetimino compound clearly indicated that cyclization had occurred as shown. In *N*-acylsydnone imines the carbonyl absorption was found[11] to be in the region 1667–1626 cm^{-1} and the corresponding ring proton resonated[11] between τ 2.00–2.37.

The corresponding *anhydro*-4-*N*-acetimino-2,3-diphenyl-1-methylimidazolium hydroxide (**7**, R = CH_3) was obtained similarly from **4** and acetyl chloride. Its spectral characteristics were consistent with those of the benzoyl derivative (see Experimental Section).

As anticipated, the action of dry hydrogen chloride on the nitrile **4** resulted in the formation of 4-amino-2,3-diphenyl-1-methylimidazolium chloride (**8**). The disappearance of the ν_{CN} 2250-cm^{-1} absorption of **4** and the presence of a ν_{NH_2} 3390-, 3250-cm^{-1} absorption, together with a singlet proton at τ 2.85, provided strong evidence for the assigned structure. Conversion of **8** into its picrate and perchlorate provided additional evidence for this structure. As **7** (R = CH_3) is the acetylated derivative of **8** minus the elements of HCl, it was possible to convert **8** into **7** (R = CH_3) by the action of acetic anhydride, followed by sodium bicarbonate. Similarly, treatment of **8** with benzoic anhydride followed by sodium bicarbonate gave **7** (R = Ph) in 71% yield. Additional evidence for the structure of the salt **8** was its behavior on mild treatment with aqueous potassium hydroxide solution. At room temperature over a short period of time, it was transformed into *N*-methyl-*N*-(N^1-phenylbenzimidoyl)acetamide (**5**).

A recent report[12] of the formation of *anhydro*-3-imino-4-methyl-5-phenyl-1,2,4-thiadiazolium hydroxide



from the action of Ag_2O on the corresponding hydroiodide is of particular interest in this area of imino derivatives of mesoionic compounds. This is the first instance in which the free base of such a compound has been isolated, and we were accordingly especially interested in studying the action of base on the compound **8**. On treatment with warm, dilute potassium hydroxide sulution, it was transformed into an isomeric product ($M\cdot^+$, *m/e* 249) with an infrared absorption band at 3275 cm^{-1}, indicative of an NH group. No carbonyl absorption was present and the nmr spectrum of the product indicated the presence of an NCH_3 group (τ 6.26), a sharp singlet at τ 3.07, aromatic absorptions at τ 2.99–2.42, and a single proton at τ 1.84 which rapidly exchanged with D_2O. This product was characterized further by conversion into its picrate and acetyl derivative which were not the same as the corresponding derivatives obtained from 4-amino-2,3-diphenyl-1-methylimidazolium chloride (**8**). This alkali-treatment product is best represented by structure **9**, 4-anilino-1-methyl-2-phenylimidazole, which could be formed by a *Dimroth-type rearrangement from* **8**. This is the first reported example of such a rearrangement in mesoionic-type systems,[13] though related interconversions of mesoionic ring systems, such as the imidazole → thiazole[4] and the 1,3,4-oxadiazole → 1,3,4-thiadiazole[14] ring system have been reported. The rearrangement product **9** was also formed by several other routes. Thus treatment of the nitrile **4** with warm potassium hydroxide solution, and also treatment of the amide **5** under similar conditions, gave **9**. It is most likely that the reaction of the nitrile **4** actually involved the intermediacy of the amide **5**. In another hydrolysis experiment, prolonged treatment of the salt **8** with aqueous potassium hydroxide over 3 days gave *N*-benzoyl-*N*-methylaminoacetanilide (**10**) which could only have arisen by hydrolysis of the rearrangement product **9** formed initially from **8**. As expected, treatment of **9** under similar conditions gave **10**.

(10) P. Brookes and J. Walker, *J. Chem. Soc.*, 4409 (1957); H. Kato, M. Hashimoto, and M. Ohta, *Nippon Kagaku Zasshi*, **78**, 707 (1957).

(11) H. U. Daeniker and J. Druey, *Helv. Chim. Acta*, **45**, 2441 (1962).

(12) J. Goerdeler and W. Roth, *Chem. Ber.*, **96**, 534 (1963).

(13) In a future communication, several other examples of Dimroth-type rearrangements [for a recent review see M. Wahren, *Z. Chem.*, **9**, 241 (1969)] in mesoionic systems will be described.

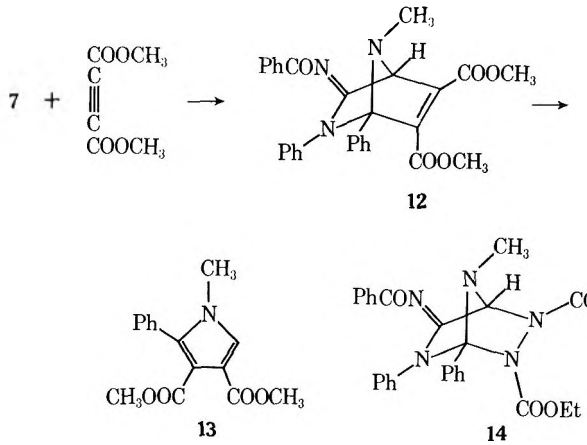
(14) A. R. McCarthy, W. D. Ollis, and C. A. Ramsden, *Chem. Commun.*, 499 (1968).

The acetyl product obtained from **9** and acetic anhydride is worthy of further comment. Mass spectral data ($M\cdot^+$, m/e 291) indicated that monoacetylation only had occurred and this was confirmed by nmr data. A sharp singlet at τ 7.49, coupled with the disappearance of the 5 H in **9** at τ 3.07 and an exchangeable proton at τ 0.13 (NH, a downfield shift of 1.71 ppm from the NH in **9**) suggested that C-acetylation had occurred. This is consistent with the known directive effects on electrophilic substitution of the imidazole nucleus.[15]

The above data are more consistent with the representation of this rearrangement product as **9** rather than as its tautomer **11**. However, in the oxazole series, analogous dipolar structures have been shown to be involved in the characteristic cycloadditions of azomethine ylides shown by Δ^2-oxazolin-5-ones.[16]

In cycloadditions utilizing mesoionic systems as 1,3 dipoles, small, stable molecules such as carbon dioxide[17] or carbon disulfide[18] are usually eliminated from the initial cycloadduct. We recently showed that *p*-tolyl isocyanate was readily lost from the initial cycloadduct formed from *anhydro*-4-hydroxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium hydroxide and dimethyl acetylenedicarboxylate,[19] and we have now found that much larger fragments may be eliminated from primary cycloadducts.

Reaction of *anhydro*-4-benzoylimino-2,3-diphenyl-1-methylimidazolium hydroxide (**7**, R = Ph) with dimethyl acetylenedicarboxylate occurred over 10 min in refluxing benzene with the formation of dimethyl 1-methyl-2-phenylpyrrole-3,4-dicarboxylate (**13**) in 38% yield. By analogy with other 1,3-dipolar cycloadditions of this type, the reaction is regarded as involving an intermediate such as **12** from which *N*-benzoyl-*N'*-phenylcarbodiimide was eliminated. No trace of this product was detected, the only other compound isolated being benzanilide. The corresponding acetyl derivative of **7** (R = CH_3) also underwent ready reaction with the dipolarophile forming **13** in 45% yield.



With ethyl azodicarboxylate **7** (R = PH) formed a stable 1:1 adduct (85% yield) represented as **14** on the basis of analytical and spectral data. The nmr spectrum showed the presence of the two ester groups and the NCH_3 group. In this case, however, the bridgehead hydrogen at C_4 absorbed in the same region as the phenyl protons, no doubt due to the effect of the *N*-benzoylimino substituent at C_5. In the corresponding 1:1 adduct from *anhydro*-4-hydroxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium hydroxide,[19] the analogous bridgehead proton was found at τ 0.18, though in the adduct from dimethyl acetylenedicarboxylate and *anhydro*-4-hydroxy-2-methylcinnolinium hydroxide[20] it occurred at τ 5.69. Ethyl azodicarboxylate also formed a 1:1 adduct with **7** (R = CH_3). Though the adduct was obtained crystalline, it was unstable and rapidly deteriorated.

Similarly dimethyl maleate formed a 1:1 adduct with **7** (R = Ph) which, on the basis of analytical data, is tentatively assigned a structure analogous to **14**. Spectral data were not sufficiently definitive to enable an unambiguous assignment of structure to be made.

Experimental Section[21]

Hydrolysis of *N*-Methyl-*N*-(*N'*-phenylbenzimidoyl)aminoacetonitrile (4). A. With 2% HCl.—The nitrile (2.5 g) was refluxed in 2% aqueous HCl (25 ml) for 45 min and, after cooling, the oily product which had solidified was removed by extraction with chloroform. It formed colorless needles, mp 164–165°, and was identified[22] as benzanilide (lit.[23] mp 163°): ν_{NH} 3350, ν_{CO} 1650 cm^{-1}. The aqueous phase was evaporated to dryness and dried thoroughly. The solid residue was then triturated with absolute ethanol and filtered giving sarcosine hydrochloride, 100 mg, mp 169° (lit.[24] mp 168–170°). The ethanol filtrate was diluted with an excess of anhydrous ether and cooled, and the resultant gummy solid was triturated with acetone whence it solidified. It crystallized from ethanol–ether as colorless shiny plates of *N*-methyl-*N*-(*N'*-phenylbenzimidoyl)acetamide hydrochloride (**5**): 0.8 g (28%); mp 192–193°; ir (KBr) 3210 (NH), 2850 ($\geq N^+-$), 1700 (CO), 1650 cm^{-1} (C=N); $\lambda_{max}^{CH_3OH}$ 225 nm (log ϵ 4.13), 197 (4.50); nmr (DMSO-d_6) τ 6.9 (s, 3, NCH_3), 5.25 (s, 2, CH_2), 2.53 (m, 10, aromatic).

Anal. Calcd for $C_{16}H_{18}ClN_3O$: C, 63.26; H, 5.93; N, 13.83. Found: C, 63.27; H, 5.97; N, 13.97.

The free base was obtained by the addition of sodium hydroxide to an aqueous solution of the hydrochloride and isolated by chloroform extraction. It crystallized from chloroform–petroleum ether (bp 60–80°) as colorless needles: mp 97–99°; ir (KBr) 3440, 3325 (NH), 1650 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 223 nm (log ϵ 4.07), 197 (4.46); nmr ($CDCl_3$) τ 6.95 (s, 3, NCH_3), 5.79 (broad s, 2, CH_2), 5.02 (broad s, 2, NH_2), 2.93 (m, 10, aromatic); $M\cdot^+$ m/e (rel intensity) 267 (39).

Anal. Calcd for $C_{16}H_{17}N_3O$: C, 71.88; H, 6.41; N, 15.72. Found: C, 72.02; H, 6.44; N, 15.83.

B. With 20% HCl.—The nitrile (2.5 g) in 20% aqueous HCl (25 ml) was refluxed for 45 min. On cooling, shiny plates (0.4 g) of benzoic acid, mp 122°, separated from the hydrolysis mixture. The filtrate was evaporated to dryness, water added, and the evaporation repeated. Absolute ethanol was then added and all traces of water were removed by several evaporations with absolute ethanol. The residue was treated with a further quantity of ethanol and the undissolved material, shown to be ammonium chloride, separated. Concentration of the ethanol solution and

(15) E. S. Schipper and A. R. Day in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp 199–203.

(16) H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Amer. Chem. Soc.*, **93**, 4340 (1970), and references cited therein; G. Kille and J. P. Fleury, *Bull. Soc. Chim. Fr.*, 4636 (1968); R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).

(17) *E.g.*, R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.*, **101**, 536 (1968).

(18) K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061 (1968).

(19) K. T. Potts and S. Husain, *J. Org. Chem.*, **35**, 3451 (1970).

(20) D. E. Ames and B. Novitt, *J. Chem. Soc. C.*, 2355 (1969).

(21) All evaporations were carried out 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 (70 eV). Melting points were taken in capillaries and microanalyses were performed by Instranal Laboratories, Inc., Rensselaer, N. Y.

(22) Standards for product equivalency were superimposable infrared spectra, less than 2° depression in a mixture melting point, and identical R_f values on tlc.

(23) F. J. Sowa and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **59**, 1202 (1937).

(24) L. Bauman, *J. Biol. Chem.*, **21**, 563 (1915).

cooling gave sarcosine hydrochloride which was removed. The ethanol filtrate was diluted with ether and the product which separated was triturated with acetone giving a dark solid material. This was dissolved in saturated sodium bicarbonate solution and yielded the impure sodium salt (*ca.* 0.5 g) of the acid 1 on evaporation to dryness.

Attempted Synthesis of *anhydro*-2,3-Diphenyl-4-hydroxy-1-methylimidazolium Hydroxide.—The acid hydrochloride prepared above, or the sodium salt of the acid, was treated, at 0° with acetic anhydride–triethylamine (3:1). Colorless needles (from benzene–petroleum ether) of *anhydro*-5-acetyl-2,3-diphenyl-4-hydroxyimidazolium hydroxide, mp 241–243° (lit.[2] mp 241–243°), were always obtained irrespective of the proportion and amount of acetic anhydride–triethylamine used: ir (KBr) 1690, 1625 cm^{-1} (CO); nmr ($CDCl_3$) τ 7.42 (s, 3, $COCH_3$), 6.05 (s, 3, NCH_3), 2.65 (m, 10, aromatic).

***anhydro*-4-Benzoylimino-2,3-diphenyl-1-methylimidazolium Hydroxide (7, R = Ph).**—The nitrile 4 (2.5 g), dry benzene (75 ml), and benzoyl chloride (1.5 g) were refluxed for 1 hr during which time the hydrochloride separated. After cooling, the solid material was treated with a 5% aqueous solution of sodium bicarbonate and a yellow product separated. It crystallized from chloroform–petroleum ether as shiny, yellow needles: 3.0 g (85%); mp 249–251°, with darkening at 230°; ir (KBr) 3170, 3040 (CH), 1580 (CO), 1540 cm^{-1} (C=N); $\lambda_{max}^{CH_3OH}$ 322 nm (log ϵ 3.92), 260 (3.98), 225 (4.31); $M\cdot^+$ *m/e* (rel intensity) 353 (42).

Anal. Calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.00; H, 5.42; N, 11.82.

When the nitrile 4 (0.6 g) in dry benzene (10 ml) and acetyl chloride (0.2 g) were stirred at room temperature for 30 min and then warmed gently for an additional 30 min, the corresponding hydrochloride separated. Addition of 5% aqueous sodium bicarbonate solution to the hydrochloride and extraction of the resulting solution with chloroform finally gave a pale yellow product. ***anhydro*-4-Acetimino-2,3-diphenyl-1-methylimidazolium hydroxide (7, R = CH_3)** crystallized from methanol–benzene as pale yellow needles: 0.6 g (85%); mp 192–193°; ir (KBr) 3400 (H_2O), 3160, 3050 (CH), 1550 (CO), 1500 cm^{-1} (C=N); $\lambda_{max}^{CH_3OH}$ 257 nm (log ϵ 3.93); nmr (DMSO-d_6) τ 6.25 (s, 3, $COCH_3$), 6.37 (s, 3, NCH_3), 2.60 (s, 5, N_3-C_6H_5), 2.70 (s, 5, C_2-C_6H_5), 2.37 (s, 1, C_5-H); $M\cdot^+$ *m/e* (rel intensity) 291 (32).

Anal. Calcd for $C_{18}H_{17}N_3O\cdot{}^3/_4H_2O$: C, 70.85; H, 5.74; N, 13.78. Found: C, 70.76; H, 5.75; N, 13.67.

4-Amino-2,3-diphenyl-1-methylimidazolium Chloride (8).—Dry hydrogen chloride was passed into a solution of the nitrile 4 (5.0 g) in anhydrous ether (150 ml) at 0°. After saturation of the reaction mixture with hydrogen chloride the product was filtered and washed several times with anhydrous ether. Crystallization from ethanol–ether gave the above salt as colorless, hygroscopic needles: ir (KBr) 3390, 3250, 1650 cm^{-1} (NH_2); nmr (DMSO-d_6) τ 6.27 (s, 3, NCH_3), 2.85 (s, 1, C_5-H), 2.52 (s, 10, aromatic), 2.04 (s, 2, C_4-NH_2, exchanged with D_2O). It was characterized by conversion into its perchlorate by treatment of its aqueous solution with 70% perchloric acid. The perchlorate separated from ethanol–ether as colorless needles: mp 181–182°; ir (KBr) 3425, 3350, 1640 cm^{-1} (NH_2); $\lambda_{max}^{CH_3OH}$ 290 nm (log ϵ 3.83).

Anal. Calcd for $C_{16}H_{16}ClN_3O_4$: C, 54.93; H, 4.58; N, 12.01. Found: C, 55.00; H, 4.65; N, 12.27.

The picrate was obtained as yellow needles from ethanol: mp 143–144°; $\lambda_{max}^{CH_3OH}$ 355 nm (log ϵ 4.19), 303 (3.96).

Anal. Calcd for $C_{22}H_{18}N_6O_7$: C, 55.38; H, 3.78; N, 17.57. Found: C, 55.24; H, 3.75; N, 17.82.

Treatment of 4-Amino-2,3-diphenyl-1-methylimidazolium Chloride with Benzoic Anhydride.—The hydrochloride (3.0 g) and benzoic anhydride (5.0 g) were heated at 150° for 1 hr. The cooled reaction mixture was triturated with benzene and the solid product was collected. It was suspended in water and treated with 10% aqueous sodium bicarbonate whence a yellow product separated. It crystallized from chloroform–petroleum ether as yellow needles, 2.5 g (70%), mp 249–251°. This was identical with 7 (R = Ph). Use of acetic anhydride in the above reaction, except that the final product was isolated by chloroform extraction, gave 7 (R = CH_3) as yellow needles, mp 192–193° (68%).

Reaction of 4-Amino-2,3-diphenyl-1-methylimidazolium Chloride with Sodium Hydroxide. A. Formation of 4-Anilino-1-methyl-2-phenylimidazole (9).—The above chloride (2.0 g) in methanol (15 ml) and KOH (1.5 g) in water (50 ml) were warmed on the steam bath for 3 hr, keeping the reaction volume constant by the addition of water. The product, which started to separate after 30 min, was collected from the cooled reaction mixture and recrystallized from benzene–petroleum ether. It separated as colorless needles: 0.8 g (46%); mp 182–184°; ir (KBr) 3280 (NH), 1620 (C=N), 1580 cm^{-1} (C=C); $\lambda_{max}^{CH_3OH}$ 265 nm (log ϵ 4.00), 232 (3.89), 203 (4.33); nmr (DMSO-d_6) τ 6.26 (s, 3, NCH_3), 3.07 (s, 1, C_5-H), 2.99–2.42 (m, 10, aromatic), 1.84 (s, 1, NH, exchanged with D_2O); $M\cdot^+$ *m/e* (rel intensity) 249 (100).

Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86. Found: C, 76.66; H, 5.95; N, 16.82.

Using this same reaction procedure, the nitrile 4 and the amide 5 were converted into 9. The picrate crystallized from ethanol as yellow needles, mp 210–213°.

B. Formation of *N*-Methyl-*N*-(*N'*-phenylbenzimidoyl)acetamide (5).—The above chloride (1.7 g) in water (40 ml) and potassium hydroxide (2.5 g) in water (40 ml) were allowed to stand for 10 min. The oily product which separated was extracted into chloroform in the usual way. Crystallization from chloroform–petroleum ether afforded colorless needles of the amide 5, 0.8 g, mp 97–99°.

C. Formation of *N*-Benzoyl-*N*-methylaminoacetanilide (10).—The hydrochloride (1.5 g) in water (10 ml) was stirred at room temperature for 3 days with aqueous potassium hydroxide (0.6 g) in water (30 ml). The crystalline product which separated crystallized from chloroform–petroleum ether as fine, colorless needles: 400 mg (51%); mp 165–166°; ir (KBr) 3300 (NH), 3150, 3100 (CH), 1710, 1650 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 242 nm (log ϵ 4.27); nmr ($CDCl_3$) τ 6.95 (s, 3, NCH_3), 5.62 (s, 2, CH_2), 2.65 (m, 10, aromatic), 0.88 (broad s, 1, NH, exchanged with D_2O); mass spectrum *m/e* (rel intensity) 176 (26), 105 (100), 77 (90).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.27; H, 5.92; N, 10.23.

5-Acetyl-4-anilino-1-methyl-2-phenylimidazole.—The 4-anilino compound 9 (400 mg) was heated at 100° with acetic anhydride (4 ml) for 3 hr. The reaction mixture was diluted with benzene and evaporated to dryness. This process was repeated using xylene until all traces of acetic anhydride were removed. The solid residue was dissolved in benzene and chromatographed on Florisil being eluted with chloroform–methanol (2%). It crystallized from benzene–petroleum ether as pale yellow silky needles: mp 149–150°; ir (KBr) 1600, 1625 (CO, C=N), 1580 cm^{-1} (C=C); $\lambda_{max}^{CH_3OH}$ 360 nm (log ϵ 4.24), 273 (4.39), 248 (sh, 4.18), 203 (4.40); nmr ($CDCl_3$) τ 7.49 (s, 3, $COCH_3$), 6.20 (s, 3, NCH_3), 2.92–2.50 (m, 10, aromatics), 0.13 (s, 1, NH, exchanged with D_2O); $M\cdot^+$ *m/e* (rel intensity) 291 (100).

Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.23; H, 5.84; N, 14.43. Found: C, 74.23; H, 5.89; N, 14.43.

Reaction of *anhydro*-4-*N*-Benzoylimino-2,3-diphenyl-1-methylimidazolium Hydroxide (7, R = Ph) with Dimethyl Acetylenedicarboxylate.—The 4-*N*-benzoylimino compound (0.7 g), dry benzene (25 ml), and the ester (0.3 g) were gently refluxed for 30 min. The reaction mixture was chromatographed on Florisil and, on elution with chloroform–methanol (98:2), a colorless crystalline product was obtained. This was found to be contaminated with benzanilide which was removed by sublimation *in vacuo* [150° (0.1 mm)]. Recrystallization of the residue from chloroform–petroleum ether afforded shiny, colorless plates of 1-methyl-2-phenylpyrrole-3,4-dicarboxylate: 0.21 g (38%); mp 117–118° (lit.[25] mp 117–118°); ir (KBr) 1710 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 262 nm (log ϵ 3.98), 215 (4.34); $M\cdot^+$ *m/e* (rel intensity) 273 (68).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.16; H, 5.56; N, 5.03.

Use of the corresponding 5-*N*-acetylimino compound in the above reaction resulted in formation of the pyrrole in 45% yield.

Reaction of 7 (R = Ph) with Ethyl Azodicarboxylate.—The *N*-benzoylimino compound (0.7 g) in benzene (25 ml) and ethyl azodicarboxylate (0.33 g) were warmed gently on the steam bath for 15 min. Evaporation of the benzene and trituration of the gummy residue with ether gave a finely crystalline product. It separated from chloroform–petroleum ether as shiny colorless plates: 0.9 g (85%); mp 187–189°; ir (KBr) 3055, 2980 (CH_3), 1750 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 295 nm (log ϵ 3.79), 260 (3.98), 220 (4.36); nmr ($CDCl_3$) τ 8.76 (t, 3, J = 7.0 Hz, CH_2CH_3), 8.71 (t, 3, J = 7.0 Hz, CH_2CH_3), 6.11 (s, 3, NCH_3), 5.80 (qt, 4, J = 7.0 Hz, CH_2CH_3), 2.66–2.0 (m, 16, aromatic and CH).

(25) K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061 (1968).

Anal. Calcd for $C_{29}H_{29}N_5O_5$: C, 66.02; H, 5.54; N, 13.28. Found: C, 65.80: H, 5.53; N, 13.19.

Registry No.—**5**, 31446-92-1; **5** free base, 31446-93-2; **7** (R = Ph), 29985-00-0; **7** (R = Me), 31489-84-6; **8**, 31446-95-4; **8** perchlorate, 31446-96-5; **8** picrate, 31446-97-6; **9**, 31446-98-7; **9** picrate, 31446-99-8; **9** (5-acetyl), 31382-26-0; **10**, 31382-27-1; **13**, 19611-52-0; **14**, 31382-29-3.

Reactions of 3-Carboxyacryloylhydrazines and the Formation of Maleimides, Isomaleimides, and Pyridazinones

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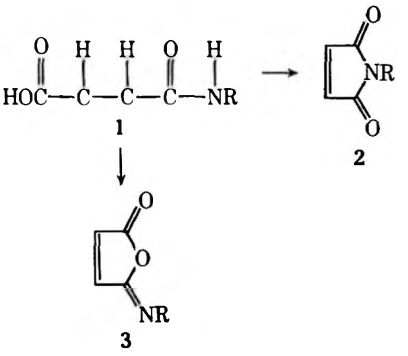
Some of the previous structure assignments for the reaction products arising from ring closure reactions of 3-carboxyacryloylhydrazines are in error. Criteria are presented for distinguishing between 3-carboxyacryloylhydrazines, isomaleimides, maleimides, and pyridazinones.

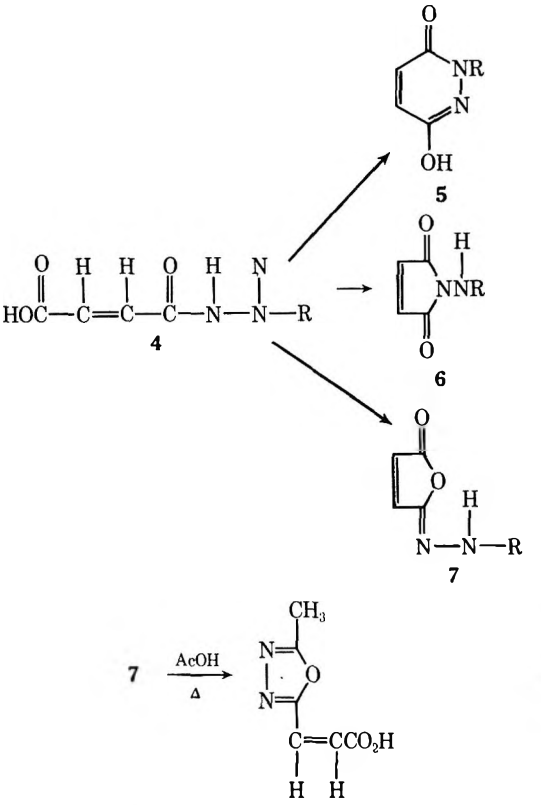
Recently, there has been a great deal of interest in the formation of N-substituted maleamic acid derivatives **1** and in their conversion to maleimides **2** and isomaleimides **3** upon dehydration[1-12] (eq 1).



(1)

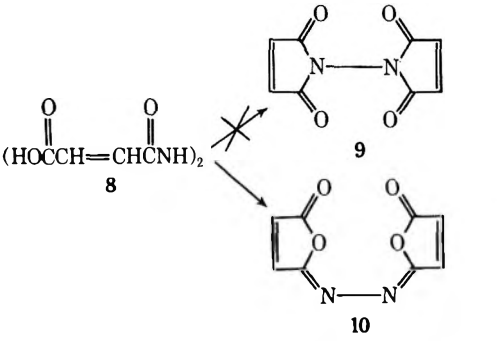
With substituted β-acryloylhydrazides **4** an additional ring closure to pyridazinones **5** may take place (eq 2). It also has been shown that **7** (R = $COCH_3$) rearranges in boiling acetic acid to a 1,3,4-oxadiazole[13-15] (eq 3).

Feuer and Rubinstein[1] suggested that the dehydration of substituted 3-carboxyacrylolylhydrazines **4** in thionyl chloride led to the corresponding substituted maleimides **6**. These structure assignments were based upon infrared absorption of the amide carbonyl group and elemental analysis. They also reported the formation of the bismaleimide **9** as the product of the dehydration of 1,2-bis(3-carboxyacryloyl)hydrazine (**8**) (eq 4).



(2)

(3)



(4)

Subsequently, Feuer and Asunskis[2] prepared what were thought to be various substituted aminomalei-

(1) H. Feuer and H. Rubinstein, *J. Amer. Chem. Soc.*, **80**, 5873 (1958).
(2) H. Feuer and J. Asunskis, *J. Org. Chem.*, **27**, 4684 (1962).
(3) W. R. Roderick and P. L. Bhatia, *ibid.*, **28**, 2018 (1963).
(4) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *ibid.*, **26**, 10 (1961).
(5) A. E. Kretov, N. E. Kyl'chitskaya, and A. F. Mal'new, *J. Gen. Chem. USSR*, **31**, 2415 (1961).
(6) D. Y. Curtin and L. I. Miller, *Tetrahedron Lett.*, 1869 (1965).
(7) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *J. Org. Chem.*, **31**, 1311 (1966).
(8) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, **31**, 1317 (1966).
(9) M. L. Ernst and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 5001 (1966).
(10) W. R. Roderick, *J. Org. Chem.*, **29**, 745 (1964).
(11) C. K. Sauers, *ibid.*, **34**, 2275 (1969).
(12) C. K. Sauers, *Tetrahedron Lett.*, 1149 (1970).
(13) A. Le Berre, J. Godin, and R. Garreau, *C. R. Acad. Sci., Ser. C*, **265**, 570 (1967).
(14) J. Godin and A. Le Berre, *Bull. Soc. Chim. Fr.*, **10**, 4210 (1968).
(15) M. Dormoy, J. Godin, and A. Le Berre, *ibid.*, **10**, 4222 (1968).

mides in order to study the effect of the substituent on their transformation to the supposed pyridazinones **5**. These workers, however, did not consider that they might be dealing with isomaleimide–maleimide or isomaleimide–pyridazinone interconversions.

More recently Hedaya and coworkers[7,8] showed that the reaction product of **8** with thionyl chloride was the biisomaleimide **10**. They also reported that 1-acetyl-2-(3-carboxyacryloyl)hydrazine reacted with acetic anhydride at room temperature to give the isomaleimide **7** (R = $COCH_3$). These results were confirmed by Le Berre and coworkers.[13] Both groups used the appearance of a typical AB pattern in the nmr spectrum to rule out the malemide structure. However, there has been disagreement between these investigators regarding the fate of **7** in acetic acid. LeBerre reported that **7** (R = $COCH_3$) was converted to an oxadiazole (eq 3), whereas Hedaya suggested that **7** was transformed to **5**.

In other recent studies Baloniak[16,17] reacted various nitrophenylhydrazine derivatives with acid solutions and reported the formation of **6** and their isomerization to **5**. These results seem anomalous when considered along with the work of Hedaya and LeBerre and the related work with maleamic acids.[3–7,10–13,18]

This work deals with a reexamination of the reaction of maleic anhydride with substituted hydrazines and of the cyclization reactions of 3-carboxyacryloylhydrazines in order to resolve the discrepancies in the literature.

Results

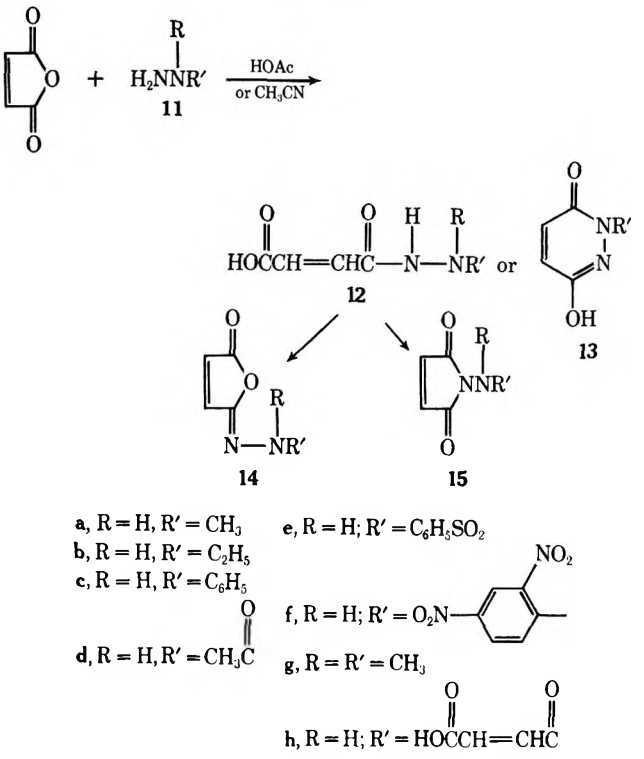
The nature of the group substituted on hydrazine and on the 3-carboxyacryloylhydrazines resulting from the reaction of hydrazines **11** with maleic anhydride plays an important part in the formation of five- or six-membered ring compounds. Electron-donating groups give the pyridazinones **13a,b** directly by the reaction of maleic anhydride with the substituted hydrazines **11a,b** (Scheme I). More neutral or electron-attracting groups give the substituted 3-carboxyacryloylhydrazines **12c–h**.

The reaction of β-acryloylhydrazines **12d–f** carrying electron-withdrawing substituents with dehydrating agents such as acetic anhydride or thionyl chloride leads to the formation of the isomaleimides **14d–f**. On the other hand, a mixture consisting of isomaleimide **14g** and maleimide **15g** was obtained with the 1,1-dimethyl compound **12g** and only polymeric material with the phenyl derivative **12c**.

The course of the reaction of **12** in acid solutions such as acetic acid again depends upon the substituent group present. In the case of electron-donating groups six-membered ring formation occurs (**12c** gives **13c**), whereas with electron-withdrawing groups maleimide formation takes place (**12d–f** gives **15d–f**). Maleimide formation also takes place when *N,N*-dimethyl-3-carboxyacryloylhydrazine (**12g**) is reacted in acid solutions.

Proof of Structure of 3-Carboxyacryloylhydrazines 12.—As shown in Table I the infrared spectra of **12** exhibit carbonyl absorption in the 1710–1695-cm^{-1} region indicating the presence of an α-β-unsaturated system.[19] The nmr spectra of **12** showed vinyl proton peaks at δ 6.3–6.5. Surprisingly, compounds **12d–f,h** having strongly electron-withdrawing groups exhibited a single peak for the vinyl protons, indicating a balanced electronic effect. The phenyl and the *N,N*-dimethyl compounds gave a typical AB pattern where the outer transitions were quite weak, indicating a small difference in chemical shift as would be expected from this type of system.

SCHEME I



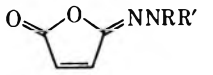
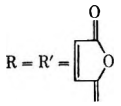
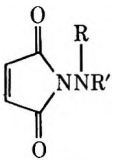
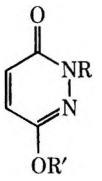
Proof of Structure of Isomaleimides 14.—The infrared spectra of isomaleimides show a strong and characteristic carbonyl absorption peak in the 1778–1790-cm^{-1} region[7], absorption in the C=N region at 1600–1650[3,7] cm^{-1}, and strong N–H absorption at 3140–3500 cm^{-1}. The nmr data (Table I) show the presence of nonequivalent vinyl protons. The acetyl derivative **14d** exhibits a typical AB pattern consistent with the reports of Hedaya[7] and LeBerre.[13] The dimethyl compound **14g** and biisomaleimide **14h** give a similar pattern. In the case of the benzenesulfonyl and 2,4-dinitrophenyl derivatives **14e** and **14f**, only half of the quartet peaks were found in dimethyl sulfoxide solution; the other half were masked by the aromatic protons. In both cases the use of chloroform as the solvent shifted the vinyl proton peaks sufficiently to confirm the presence of a quartet. The isomaleimide vinyl protons had coupling constants J = 5.5–6.0 cps.[11]

Proof of Structure of Maleimides 15.—The infrared spectra of the maleimides show a broad carbonyl absorption at 1705–1715 cm^{-1} which is characteristic of imides.[4,7,14] The carbonyl absorption of six-membered ring pyridazines is found at lower frequencies (Table I). Thus, previously reported pyridazinones[1,2,7] are most probably maleimides. The nmr spectra show conclusively that the maleimide structure is correct since

(16) S. Baloniak, *Rocz. Chem.*, **41**, 1143 (1967).
(17) S. Baloniak, *ibid.*, **42**, 1231 (1968).
(18) These transformations are currently being investigated by Mr. Michael Parnarouskis.
(19) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 168.

TABLE I

SPECTRAL PROPERTIES OF 3-ACRYLOYLHYDRAZINES, ISOMALEIMIDES, MALEIMIDES, AND PYRIDAZINONES

R	R′	Registry no.	Ir, cm⁻¹,[a] CO stretch	Nmr[b-d] Olefinic protons, δ	J, Hz	Aromatic protons, δ	Substituent protons, δ
			3-Acryloylhydrazines				
H	C_6H_5	31413-85-1	1695 (s)	6.95 d, 6.34 d	10	7.45–6.75 m	
H	CH_3CO	17789-76-3	1688 (s)	6.50 s			1.97 s ($COCH_3$, 2.9 H)
H	$C_6H_5SO_2$	31413-87-3	1688 (s)	6.36 s		8.1–7.7 m	
H	$2,4\text{-}(NO_2)_2C_6H_3$	31413-88-4	1710 (s)	6.55 s		10.12–7.42 m	
H_3C	CH_3	10191-43-2	1700 (m)	6.40, 6.37			2.64 s [$N(CH_3)_2$, 6.1 H]
H	$HO_2CCH{=}CHCO$	5343-00-0	1679 (br)	6.52 s			
			Isomaleimides 				
H	CH_3CO	6903-87-3	1778	7.79 d, 6.79 d	5.5		1.98 s ($COCH_3$, 3 H)
H	$C_6H_5SO_2$	30986-27-7	1790	7.70 d, 6.79 d	5.5	7.9–7.4 m	
				7.08 d, 6.23 d	5.5[e]	8.2–7.2 m	
H	$2,4\text{-}(NO_2)_2C_6H_3$	31413-91-9	1785	7.95 d, 6.97 d	6	9.0–7.8 m	
				7.52 d, 6.58 d	6[f]	9.2–7.9 m	
H_3C	CH_3	31413-92-0	1783	7.14 d, 6.07 d	5.5[g]		3.20 s [$N(CH_3)_2$, 6 H]
		6990-21-2	1790	8.01 d, 7.12 d	6[h]		
			Maleimides 				
H	CH_3CO	20311-07-3	1715	7.08 s			1.89 s ($COCH_3$, 3 H)
H	$C_6H_5SO_2$	30986-29-9	1715	6.86 s		7.8–7.3 m	
H	$2,4\text{-}(NO_2)_2C_6H_3$	20970-35-8	1715	7.30 s		8.90–7.35 m	
CH_3	CH_3	10270-11-1	1705	6.62 s			2.87 s [$N(CH_3)_2$, 6.1 H]
			Pyridazinones 				
H	H	10071-13-3	1660	7.02 s			
CH_3	H	10071-37-1	1660	7.20 d, 7.04 d	10		3.57 s (CH_3, 3.2 H)
C_2H_5	H	31414-00-3	1664	7.36 d, 7.19 d	10		4.08 q (CH_2, 2 H), 1.32 t (CH_3, 3 H)
C_6H_5	H	1698-54-0	1650	7.10 d, 7.0 d	10	7.68–7.25 m	
C_2H_5	CH_3CO	31414-01-4	1660	7.28 d, 6.92 d	10		3.99 q (CH_2, 2 H), 2.15 s ($COCH_3$, 3 H), 1.09 t (CH_3, 2 H)

[a] Run as a Nujol mull. [b] Parts per million. [c] All spectra were run in DMSO-d_6 unless indicated otherwise. [d] d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet. [e] Run in $CDCl_3$ at 66°. [f] Run in $CDCl_3$ at room temperature. [g] Run in CCl_4; data were obtained from a mixture of maleimide and isomaleimide by cancelling out maleimide values. [h] Run in DMSO-d_6 at 100°.

only a single peak is found in the vinyl region. Ferric chloride tests on all the maleimides were negative.

Proof of Structure of 6-Hydroxy-3(2*H*)-pyridazinones 13.—The carbonyl stretching frequency for the pyridazinones **13a–c** appears in the 1650–1670-cm^{-1} region (Table I). These data do not agree with those tabulated previously.[1,7] The previous data reported absorptions at 1740–1710 cm^{-1} which are typical for maleimides and are at a much higher frequency than would be expected for the amide carbonyl in six-membered rings.[20]

The nmr spectra of these compounds exhibit a typical AB pattern for the vinyl protons and show coupling constants J = 9.5–10 cps. The 1,2-dihydro-3(2*H*)-pyridazinone exhibits a singlet in the vinyl region because of the equivalency of the protons due to rapid tautomerization.[21] All pyridazinones were acidic and their molecular weight could be determined by potentiometric titration. They gave a positive ferric chloride test typical for phenols and enols. Further proof of structure for the pyridazinones was the reaction of these compounds with acetic anhydride to give the corresponding acetoxy derivatives.

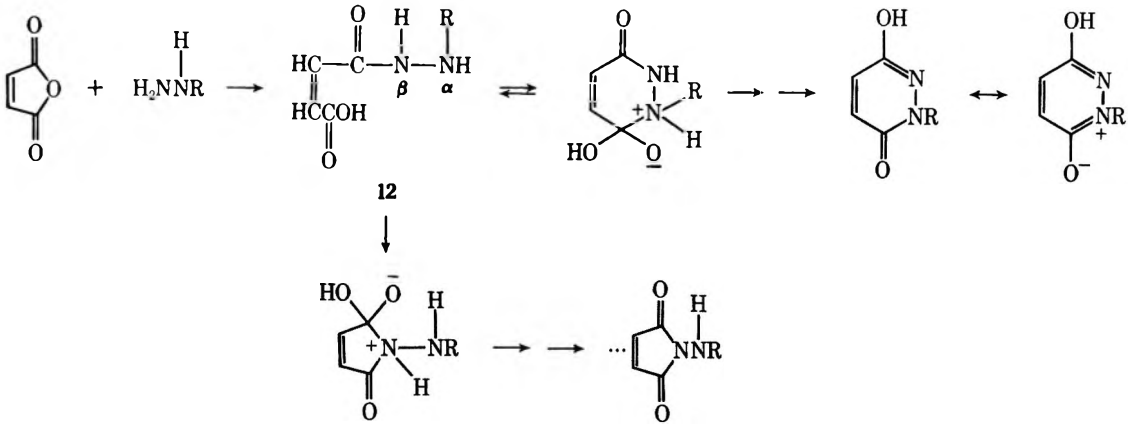
Discussion

The reaction of maleic anhydride and hydrazine in acetic acid or acetonitrile leads to the formation of β-

(20) See ref 19, p 213.

(21) A. R. Katritzky and A. T. Waring, *J. Chem. Soc.*, 1523 (1964).

SCHEME II



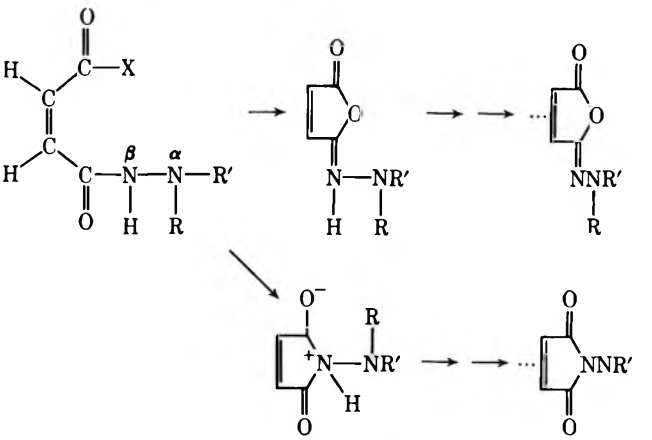
acryloylhydrazines **12** or pyridazinones **13** depending upon the electronic (or perhaps steric) environment of the nitrogen atom. This is not too surprising since the two structures may be considered as ring–chain tautomers[22] and the equilibrium between the pair in each case would be expected to depend upon the nucleophilicity of the α nitrogen atom (Scheme II). In the case of neutral or electron-withdrawing substituents the open chain tautomer is favored.

The reaction of **12** in acid solutions upon heating involves conditions which probably favor the ring tautomer by driving the equilibrium to completion *via* subsequent dehydration steps. This reaction leads to five- or six-membered ring formation depending upon the nucleophilicity of the α or β nitrogen atom (Scheme II). It has been suggested that such a reaction gives the thermodynamically favored reaction product[8,23] and hence the more stable five- or six-membered ring. In the case of electron-donating groups this would most likely be the resonance-stabilized pyridazinone ring, whereas with electron-withdrawing groups the maleimides might be expected to be more stable.

The reaction of β-acryloylhydrazines and related compounds with dehydrating agents, *i.e.*, acetic anhydride,[1,2,11] thionyl chloride,[1,2,7] and trifluoroacetic anhydride,[7,10] probably occurs with intermediate mixed anhydride formation as has been suggested for previously described dehydrations.[8,11,24]

Under these conditions the competition which takes place involves an attack by the β nitrogen on the carbonyl oxygen of the amide on the mixed anhydride carbonyl carbon atom (Scheme III). Attack by oxygen is favored and the reaction proceeds with the formation of the kinetically favored isomaleimide ring.[4,11] The substituent group on the α nitrogen again plays a role in the reaction since with the *N*,*N*-dimethyl derivative **12g** a mixture consisting of the isomaleimide and maleimide was obtained. This result was unexpected since Sauers in her study[11] has shown that in the case of *N*-arylmaleamic acids the ratio of maleimide to isomaleimide increased with decreasing electron density on the benzene ring. It may be that the influence of the nitrogen substituent in hydrazines plays a markedly different role from that of directly substituted maleamic acids.

SCHEME III



X = CH_3CO_2, CF_3CO_2, OSOCl

Experimental Section

All infrared spectra were obtained on a Beckman IR-10 spectrometer using Nujol mulls. The nmr spectra were obtained on Varian A-60 and Perkin-Elmer R-20 spectrometers. The data are shown in Table I. Melting points are corrected.

Preparation of Hydrazines 11.—All hydrazines were prepared by known methods or purchased commercially. The following hydrazines were prepared by the methods indicated in the literature or by slight variations of these methods: methylhydrazine,[25,26] ethylhydrazine,[25,27] acetic acid hydrazide,[28] benzenesulfonic acid hydrazide.[29]

Preparation of 3-Carboxyacryloylhydrazines 12.—These compounds were prepared by the methods indicated in the literature (All compounds were purified after preparation and gave neutralization equivalents indicating better than 98% purity. The maleic anhydride was recrystallized from chloroform before use.): 1-phenyl-2-(3-carboxyacryloyl)hydrazine,[30] 1-(2,4-dinitrophenyl)-2-(3-carboxyacryloyl)hydrazine,[2] 1-acetyl-2-(3-carboxyacryloyl)hydrazine,[1] 1-benzenesulfonyl-2-(3-carboxyacryloyl)hydrazine,[1] 1,1-dimethyl-2-(3-carboxyacryloyl)hydrazine,[30] 1,2-bis(3-carboxyacryloyl)hydrazine.[1]

Preparation of Isomaleimides 14.—The isomaleimides were prepared by the methods indicated in the literature except as noted (The methods used were those described by the authors for the preparation of maleimides. Thionyl chloride and acetic anhydride were distilled before use.): *N*-acetylaminoisomaleimide,[2] *N*-benzenesulfonylaminoisomaleimide,[2] 1-(2,4-dinitrophenyl)aminoisomaleimide,[2] *N*,*N*′-biisomaleimide.[1]

(22) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).
(23) H. Rubinstein, Ph.D. Dissertation, Purdue University, 1958, p 24.
(24) R. Paul and A. S. Kende, *J. Amer. Chem. Soc.*, **86**, 4162 (1964); D. V. Kashelikar and C. Ressler, *ibid.*, **86**, 2467 (1964).
(25) H. H. Watt, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 395.
(26) A. Graefe, U. S. Patent 2,962,532 (1960).
(27) A. N. Kost and R. S. Sagetullin, *Zh. Obshch. Khim.*, **33**, 867 (1963).
(28) T. Curtius and T. F. Hoffman, *J. Prakt. Chem.*, [2] **53**, 513 (1896).
(29) T. Curtius and F. Lorenzen, *ibid.*, **58**, 166 (1898).
(30) K. Eichenberger, *et al.*, *Helv. Chim. Acta*, **37**, 837 (1954).

1,1-Dimethylaminoisomaleimide (14g) and *N,N*-Dimethylaminomaleimide (15g).—*N,N*-Dimethyl-2-(3-carboxyacryloyl)-hydrazine (5.0 g) was slowly added to 120 ml of acetic anhydride, the mixture was stirred under anhydrous conditions for 48 hr, and the solvent was removed *in vacuo*. The residue was extracted with four 25-ml portions of petroleum ether (bp 30–60°) and the combined ether extracts were concentrated to about 25 ml giving yellow crystals. Recrystallization from petroleum ether gave 2.12 g of a product, mp 58–59°. The nmr data (Table I) showed this to be a mixture of maleimide and isomaleimide in the ratio of 2:1.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.43; H, 5.71; N, 20.00. Found: C, 51.15; H, 5.75; N, 19.91.

A mixture of the maleimide and isomaleimide (0.80 g) was refluxed for 2 hr in glacial acetic acid. Work-up of the resulting solution gave pure maleimide (0.66 g).[31]

Preparation of Maleimides 15.—The maleimides were prepared by the methods described for the preparation of the pyridazinones:[1,2] *N*-acetylaminomaleimide,[1,8] *N*-benzenesulfonylaminomaleimide,[2] and *N*-(2,4-dinitrophenyl)aminomaleimide.[2]

N,N-Dimethylaminomaleimide (15g).—Glacial acetic acid (100 ml) was added to 5.0 g of *N,N*-dimethyl-2-(3-carboxyacryloyl)hydrazine. The mixture was refluxed for 2 hr during which time the color changed from light green to light red. The resulting solution was concentrated *in vacuo* and the remaining oil was extracted with four 10-ml portions of petroleum ether (bp 30–60°). The combined ether extracts were concentrated and gave yellow crystals which after recrystallization from petroleum ether gave 1.6 g of a yellow powder, mp 83–84°.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.43; H, 5.71; N, 20.00. Found: C, 51.28; H, 5.83; N, 20.14.

2-Ethyl-6-hydroxy-3(2*H*)-pyridazinone (13b).—Glacial acetic acid (150 ml) and maleic anhydride (7.9 g) were mixed and 4.3 g of ethylhydrazine was added dropwise over 5 min while stirring and keeping the temperature below 30°. The solution turned light green and then yellow during the addition. Stirring for 15 min, concentrating *in vacuo*, and recrystallizing the resulting solid from 95% ethanol gave 3.0 g of **13b**, mp 143.5–145°.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.43; H, 5.71; N, 20.00; neut equiv, 140. Found: C, 51.72; H, 5.91; N, 20.25; neut equiv, 138.8.

2-Ethyl-6-acetoxy-3(2*H*)-pyridazinone.—The pyridazinone **13b** (0.3 g) was added to 25 ml of acetic anhydride and refluxed for 1 hr, and the solvent was removed *in vacuo*. The residue was recrystallized from hexane giving 0.3 g of product, mp 76–77°.

Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.49; N, 15.38. Found: C, 52.89; H, 5.60; N, 15.33.

2-Methyl-6-hydroxy-3(2*H*)-pyridazinone (13a).—Following a similar procedure as described for the preparation of **13b** gave **13a**, mp 215–216° (lit.[30] mp 210–211°). Acetonitrile was also found to be a suitable solvent for the reaction.

Anal. Calcd for $C_5H_6N_2O_2$: C, 47.63; H, 4.80; N, 22.22. Found: C, 47.56; H, 4.68; N, 22.46.

2-Methyl-6-acetoxy-3(2*H*)-pyridazinone melted at 90.5–92.0° (benzene).

Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.91; H, 4.76; N, 16.48.

2-Phenyl-6-hydroxy-3(2*H*)-pyridazinone (13c).—The procedure similar to that described for **13b** gave 2.3 g of **13c**, mp 262–263° (lit.[32] mp 259–260°).

Registry No.—2-Methyl-6-acetoxy-3(2*H*)-pyridazinone, 31443-72-8.

Acknowledgment.—One of the authors (H. R.) is indebted to the National Science Foundation for their support of some of this work by an NSF academic year extension grant for 1969–1970. We would like to thank Dr. Arthur C. Waterson and Dr. John B. Grutzner for their helpful discussions of the nmr data during the preparation of this manuscript.

(31) We are indebted to Mr. Michael Parnarouskis of Lowell Technological Institute for providing this data in response to the suggestion of one of the referees.

(32) S. Druey, *et al.*, *Helv. Chim. Acta*, **37**, 510 (1954).

Studies in Nonpyridinoid Aza-Aromatic Systems. II. Reactions of the Anions of Benzo[*b*][1]pyrindine and Its 1,2-Dihydro Derivative[1]

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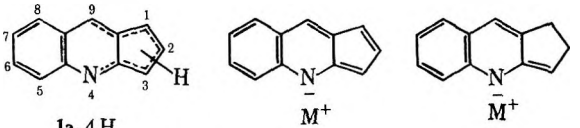
The reactivities of the anions of benzo[*b*][1]pyrindine (**1**) and of its 1,2-dihydro derivative **4** toward electrophilic reagents, such as methyl iodide, 9-fluorenone, and benzophenone, were investigated. The azulene-like, delocalized anion **2** underwent only C-methylation at C_1 and C_3 in almost equal proportions; the 1,2-dihydro anion **3** underwent exclusive methylation at C_3. Both anions reacted with benzophenone in a reversible fashion at C_3 and probably also at the nitrogen center to form a labile aminocarbinolate. The behavior of **2** is in accord with the chemical behavior expected of a nitrogen isostere of an azulene. Access to derivatives of the benzo[*b*][1]pyrindine system, starting from **4**, was gained by the synthesis of 3-methylene derivatives of **4**, followed either by a dehydrogenation with DDQ to yield a fulvene **13** or by base-promoted hydrogen transfer to provide a pyrindine **28**. Finally, abortive and partially successful attempts to dehydrogenate 1,2-dihydro anion **3** did uncover an apparently general, alternative approach to 3-methylene derivatives of **4**.

The previous study of the synthesis and tautomeric character of benzo[*b*][1]pyrindine (cyclopenta[*b*]quinoline)[1] was prompted by an interest in the aromatic character of the 4H tautomer **1a**. Being a nitrogen isostere of 5,6-benzazulene, **1a** might be expected[2] to undergo electrophilic attack in the five-membered ring and nucleophilic attack in the six-membered nitrogen ring. The latter ring would be a six-π-electron counterpart of the azulene's cyclohepta ring. Since less than 1% of this 4H tautomer is present in benzo[*b*][1]pyrindine, it seemed appropriate to convert the mixture of 1H, 3H, and 4H benzo[*b*][1]pyrindines into their common anion **2** and to examine its chemical behavior toward certain electrophiles. Furthermore, a parallel consideration of its 1,2-dihydro derivative **3** merited



1a, 4 H
b, 1 H and 3 H

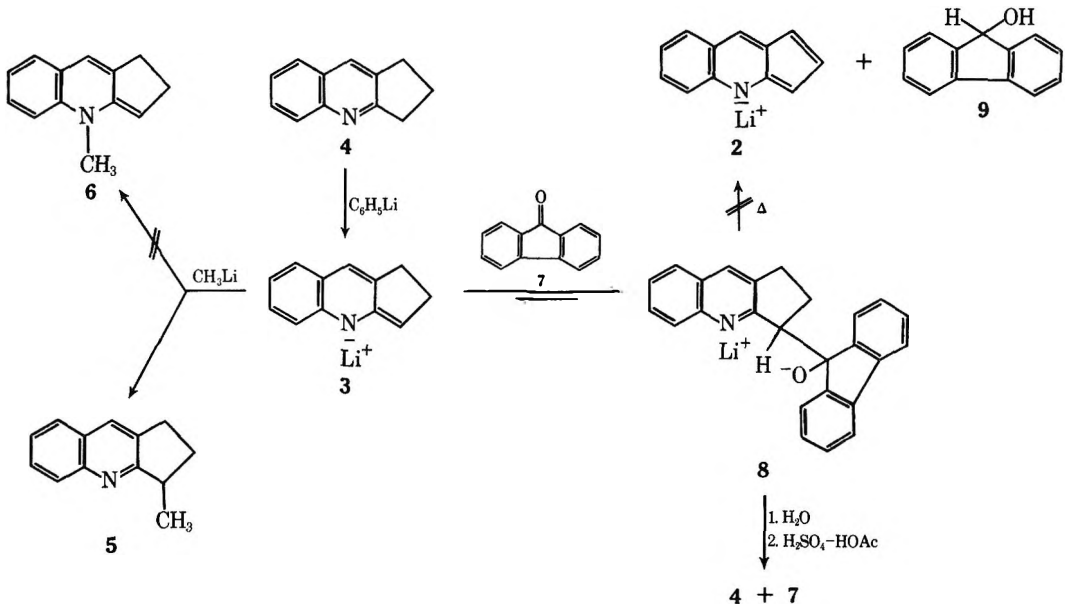
2 **3**

attention, in order to compare the chemical responses of a derivative with disrupted conjugation. At the same

(1) *Cf.* J. J. Eisch and F. J. Gadek, *J. Org. Chem.*, **36**, 2065 (1971).

(2) D. Lloyd, "Carbocyclic Nonbenzenoid Aromatic Compounds," Elsevier, New York, N. Y., 1966.

SCHEME I



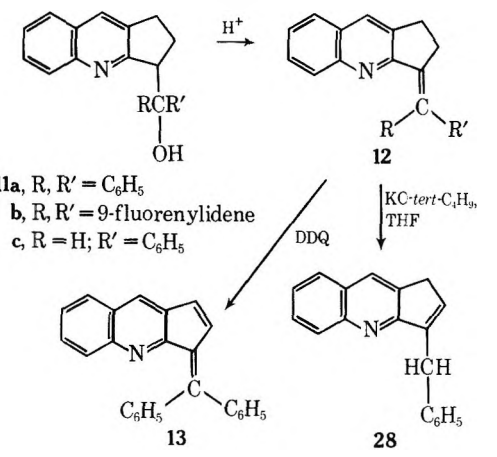
time, the possibility of converting anion **3** or a derivative into the benzo[*b*][1]pyridine system by means of 1,2 dehydrogenation was attractive for making such azulene-like aromatic systems more accessible. This report, therefore, describes the behavior of the delocalized anions *2* and **3** toward ketones and toward methyl iodide and recounts both successful and abortive attempts to dehydrogenate derivatives of **3**.

Results and Discussion

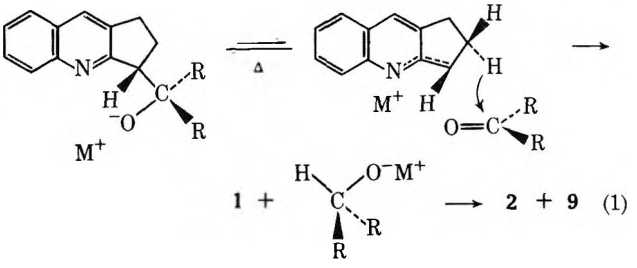
The lithium enaminate salt of 2,3-dihydro-1*H*-benzo[*b*][1]pyridine (**3**, M = Li) could be prepared in essentially quantitative yield by treating **4** with phenyllithium at 0–25°.[3a] The magnesium salt formed upon refluxing **4** with phenylmagnesium bromide in benzene solution. The pale yellow suspension of **3** reacted cleanly with methyl iodide to furnish a 90% isolated yield of 2,3-dihydro-3-methyl-1*H*-benzo[*b*][1]pyridine (-cyclopenta[*b*]quinoline, **5**) whose nmr spectrum displayed the expected three-proton doublet due to the methyl group at C_3. The presence of any considerable amount of the N-methylated product, 2,4-dihydro-4-methyl-1*H*-cyclopenta[*b*]quinoline (**6**), could be ruled by the absence of any sharp singlet in the 2.70–2.75-ppm region, where **6** is known to display its N–CH_3 resonance.[3b] Furthermore, the formation of **6** in the methylation reaction and its thermal rearrangement to **5** upon distillative isolation are unlikely, since **6**, prepared by the conventional treatment of **4** methiodide with alkali, could be distilled under nitrogen without decomposition[3b] (Scheme I).

The interaction of the lithium enaminate salt **3** with aromatic ketones, such as benzophenone[3b] and 9-fluorenone, was of twofold interest; not only did the resulting adducts (*e.g.*, **8**) promise to lead to benzo[*b*][1]-pyrindines in practical steps (*cf.* Scheme II), but hopefully these ketones might dehydrogenate **3** directly by hydrogen transfer. Since the addition of either benzophenone or 9-fluorenone to **3** proved to be reversible,

SCHEME II



it was reasoned that eventually hydride transfer might be able to compete[4] (eq 1). Although no such hydride



transfer was observed with the lithium salt **3** and benzophenone or 9-fluorenone (Scheme I), a significant amount of reduction (10–20%) was achieved when the magnesium salt of **3** (M = MgZ) was heated with benzophenone.[5] Unfortunately, the method is unsuitable for the preparation of the benzo[*b*][1]pyridine system (**1**, R = H), because the proportion of hydride transfer is modest and since it is now known that **1** cannot survive prolonged contact with strong bases.[1]

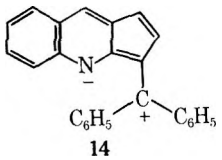
(3) (a) *Cf.* K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931), for the behavior of the lithium salt of 2-methylquinoline toward ketones and alkyl halides; (b) J. J. Eisch and F. J. Gadek, unpublished work.

(4) *Cf.* H. Gilman and C. W. Bradley, *J. Amer. Chem. Soc.*, **60**, 2335 (1938), for the ready loss of lithium hydride from organolithium compounds.

(5) *Cf.* M. S. Kharasch and S. Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

In attempting to convert such carbinols to fulvenes related to the benzo[*b*][1]pyrindine nucleus, an interesting consequence of steric hindrance to ring coplanarity was uncovered. The synthetic approach required the dehydration of the carbinol to the 3-methylene derivative of **4** and the dehydrogenation of the latter by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to yield the completely unsaturated fulvene (Scheme II). With the carbinol derived from 9-fluorenone (2,-3-dihydro-3-(9-hydroxy-9-fluorenyl)-1*H*-cyclopenta[*b*]-quinoline, **11b**), however, even mild acid treatment led only to decomposition into **4** (β-quinindane) and **7** (Scheme I). No dehydration into the 3-methylene derivative could be effected with a wide variety of experimental procedures. In contrast, the adduct from benzophenone (2,3-dihydro-α,α-diphenyl-1*H*-cyclopenta[*b*]quinoline-3-methanol, **11a**) could be dehydrated to **12a** in satisfactory yield by use of a warm solution of concentrated sulfuric acid in glacial acetic acid. Admittedly, even here some reversal to **4** and benzophenone occurred as a side reaction. The dehydration of **11b** to yield **12b** apparently is strongly disfavored by the steric repulsion between the C–H bond at C_1 of the coplanar fluorenylidene group and the (protonated) nitrogen of the quinoline ring. With **12a** the dehydration is possible, because the phenyl group syn to the (protonated) nitrogen can rotate into a conformation where its plane is at a right angle to that of the quinindane nucleus.

Once compounds of type **12** were obtained, however, they could be smoothly converted into derivatives of the benzo[*b*][1]pyrindine nucleus. The 1,2 dehydrogenation of **12a** with DDQ to yield **13** illustrates one successful approach; the isomerization of **12c** to **28** under the agency of potassium *tert*-butoxide also proved to be practical. In the latter case, a pyrindine anion of type **2** is undoubtedly an intermediate, as is evident by the deep violet color present before hydrolysis. In the former case, the bathochromic shift observed in passing from **12a** to **13** can be ascribed to the importance of resonance contributions, such as **14**, in lowering the

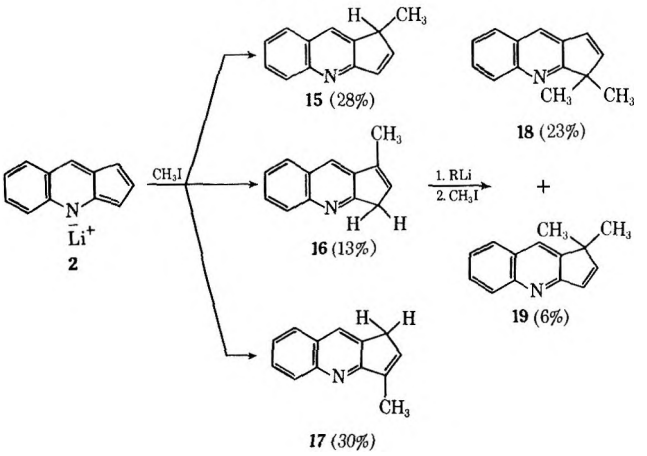


14

energy of $\pi \rightarrow \pi^*$ transitions. Since the conjugate acid of **14** might be expected to be formed in strong acid and thereby to accentuate the spectral shift, it should be noted that no bathochromic shift in the orange color of **13a** was observed, even in concentrated sulfuric acid. Furthermore, a red picrate was obtained, rather than the expected yellow form. The weak basicity of **13a** and its red complex with picric acid are reminiscent of the behavior of carbazole.[6] Stuart–Briegleb models show that the phenyl group syn to the nitrogen could easily block protonation by strong acids. Presumably the picric acid forms instead a π complex with the benzopyrindine nucleus.

Compared with the behavior of the lithium salt **3** of β-quinindane (**4**), the lithium salt of benzo[*b*][1]pyrindine (**2**) reacted very indiscriminantly with 1 equiv of methyl iodide. Due to the rapidity with which the monomethylbenzo[*b*][1]pyrindine products (**15**, **16**, and **17**) themselves formed anions and underwent methylation, a mixture of monomethylated (71%) and dimethylated (29%) benzopyrindines was obtained by distillation. Based upon known spectral shifts for such systems and relative shifts reported for methylindenes, the nmr spectrum of this mixture could be used to verify the presence of 28% of the 1-methyl-1H (**15**), 13% of the 1-methyl-3H (**16**), and 30% of the 3-methyl-1H (**17**) derivatives; in addition, 23% of the 3,3-dimethyl-3H (**18**) and 6% of the 1,1-dimethyl-1H (**19**) derivatives were estimated to be present (Scheme III).

SCHEME III



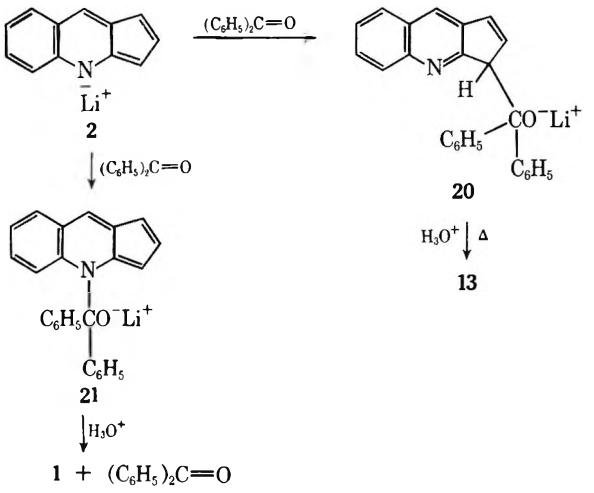
2

Interestingly, the total of all C_3 mono- and dimethylated products was 53% *vs.* 47% for C_1 methylation. Possible isomers which were not detected, such as 3-methyl-1H and 1,3-dimethyl-1H (or -3H) derivatives, might have been present in subordinate amounts. Moreover, since this nmr analysis was performed on a representative distilled sample, the tendency of benzopyrindines to polymerize thermally[1] might have led to losses of small amounts of certain isomers during distillation. In the one case where both the 1H and 3H tautomers were detected and measured (1-methybenzo-[*b*][1]pyrindines, **15** and **16**), the ratio of the 1H and 3H isomers, 62:38, compared favorably with the equilibrium ratio of tautomers for benzo[*b*][1]pyrindine itself, 67:33.[1] In any event, the results support the conclusion that the electrophilic methyl iodide seems to attack C_1 and C_3 of **2** with almost equal facility but that the lithium salt of **17** undergoes further methylation faster than the lithium salt of **15** or **16**.

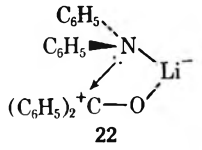
Treatment of the red lithium salt of benzo[*b*][1]-pyrindine (**2**) with benzophenone was accompanied by the appearance of a vivid purple color, but subsequent hydrolytic work-up yielded much recovered benzophenone. Careful column chromatography led to the isolation of 14% of **13** in the form of its picrate. Apparently the carbinol precursor **20** underwent dehydration under the action of acid (*cf.* **11a** → **12a**). The generation of the intense purple color during the reaction proper can best be explained by a competing N-alkylation leading to carbinol amide salt **21**, whose chromophoric system would be the same as the known, purple-colored 4*H*-benzo[*b*][1]pyrindine[1] and its 4-methyl derivative[3] (Scheme IV). Failure to isolate the

(6) S. Coffey, Ed., "Rodd's Chemistry of Carbon Compounds," Vol. III, Elsevier, New York, N. Y., 1964, p 123.

SCHEME IV



carbinolamine can be ascribed to the ready regeneration of benzo[*b*][1]pyrindine and benzophenone from **21** upon hydrolytic work-up. An alternative explanation can be drawn from the studies of Wittig and Wulff,[7] who observed that the colorless components, benzophenone and lithium diphenylamide, formed a red, diamagnetic 1:1 complex, possibly of the charge-transfer type, whose structure most reasonably was that of the "ate" salt **22**. Titrimetric discharge of the red



22

color with methanol was followed by the quantitative recovery of the ketone and the amine. In the present situation it is not only likely that **21** reverts to its components upon hydrolysis, but also that **20** is labile as well (*cf.* reversibility of carbinolates such as **11a** and **11b**, eq 1).

In summarizing the comparative behavior of anions **2** and **3**, then, it is seen that essentially only C-methylation occurs with methyl iodide and on those sites of benzo[*b*][1]pyrindine which are analogous to the C_1 and C_3 sites of azulene. For both azulene and its nitrogen counterpart (**1** and **2**), these are just those carbon atoms where the π-electron density distributions would favor electrophilic attack. For benzophenone, only products of C_3-alkylation could be isolated from either anion **2** or **3**. It is quite credible that a N-alkylation occurred with the benzopyrindine anion **2** because of the purple color of the reaction solution. With its dihydro anion **3**, such N-alkylation may also have occurred, since the yield of carbinol **11a** amounted only to 68–70%, despite prolongation of reaction times. With either anion, of course, the nitrogen atom would have the highest electron density and hence be prone to reversible alkylation.

Finally, the results of some unsuccessful attempts to convert the dihydrobenzopyrindine anion **3** into the benzopyrindine system merit brief comment. Predicated on the known tendency of certain organolithium compounds to eliminate lithium hydride upon heating,[4] suspensions of **3** were heated in refluxing xylene with hope of forming **1** or its anion **2**. However, there was no significant evidence of hydride formation nor any hydrogen gas evolution (*i.e.*, from LiH to **1a**). Heating **3** with triphenylborane, which hopefully would complex at C_3, did yield a small amount of hydride elimination in the form of a complex with the triphenylborane but this route was impractical as an approach to the parent benzopyrindine. Therefore, to foster boration at C_3, the anion **3** was treated with phenylboron dichloride with the intention of oxidizing the resulting 3-bora-2,3-dihydro derivative **23** with trimethylamine oxide.[8] The 3-hydroxy derivative **24** expected upon hydrolysis would then serve as an excellent source of **1** through an established dehydration.[1] However, no trace of **24** was formed by attempted oxidation in refluxing benzene and in refluxing toluene a 38% yield of only 3-methylene-2,3-dihydro-1*H*-benzo[*b*][1]pyrindine (**25**) was realized instead. The failure to observe the formation of any 3-hydroxy derivative **24** convincingly rules out any C_3-boration (**23**) of **3** with phenylboron dichloride and hence favors only N-boration (**26**) (Scheme V). The formation of **25** from **26** can be explained by the slow thermal decompcsition of trimethylamine oxide above 100° to yield formaldehyde[9] and the reaction of the latter with **26**. The generality of the reaction of **26** with carbonyl reagents to yield methylene derivatives of β-quinindane directly was supported by treating **26** with benzophenone. The resulting 28% yield of **12a** in this single procedure compares favorably with the 38% overall yield for the usual two-step method (**3** → **11a** → **12a**). Again the absence of any benzhydrol among the products argues against any hydride transfer by **26** (*cf.* eq 1). Utilization of this approach for the synthesis of 3-methylene derivatives of benzo[*b*][1]pyrindine and a study of their behavior under nucleophilic attack will be the subject of a subsequent report.

Experimental Section[10]

Lithium Salt of 2,3-Dihydro-1*H*-cyclopenta[*b*]quinoline (3, 6,7-Dihydro-5*H*-benzo[*b*][1]pyrindine). A. With Methyl Iodide.—The tan-colored slurry of **3** was prepared by treating 8.45 g (50.0 mmol) of **4** in 100 ml of dry benzene with 60 mmol of phenyllithium in 75 ml of ether at 0°. After being stirred at 25° for 3 hr, the suspension was recooled to 0° and treated with 6.42 g (60.0 mmol) of methyl iodide in 50 ml of dry benzene. The dark brown mixture was stirred at 25° overnight and then refluxed for 2 hr. After the usual hydrolytic work-up the isolated crude product was distilled to yield 8.21 g (90%) of colorless 2,3-dihydro-3-methyl-1*H*-cyclopenta[*b*]quinoline (**5**), bp 113–117° (0.64 mm), which turned yellow upon standing but did not solidify. A second distillation provided a colorless sample: bp 111° (0.37 mm). Spectral data: ir λ_{max}^{neat} 9.8, 10.5, 11.0, 11.6, 12.7, and 13.3 μ; nmr (CCl_4) 1.46 (d, J = 7 Hz, CH_3), 2.0–2.7 (m, CH_2), 2.75–3.5 (m, CH, CH_2), 7.2–7.75 (m, 4 H), 8.1–8.25 ppm (d, 1 H). The picrate was composed of yellow granules: mp 182.5–184.5°; nmr (CF_3CO_2H) 1.6 ppm (d).

Anal. Calcd for $C_{13}H_{13}N$: C, 85.20; H, 7.15; N, 7.64. Found: C, 85.40; H, 7.49; N, 7.47.

B. With 9-Fluorenone.—To a tan slurry of **3**, prepared from 100 mmol of **4** according to the foregoing procedure, was added a

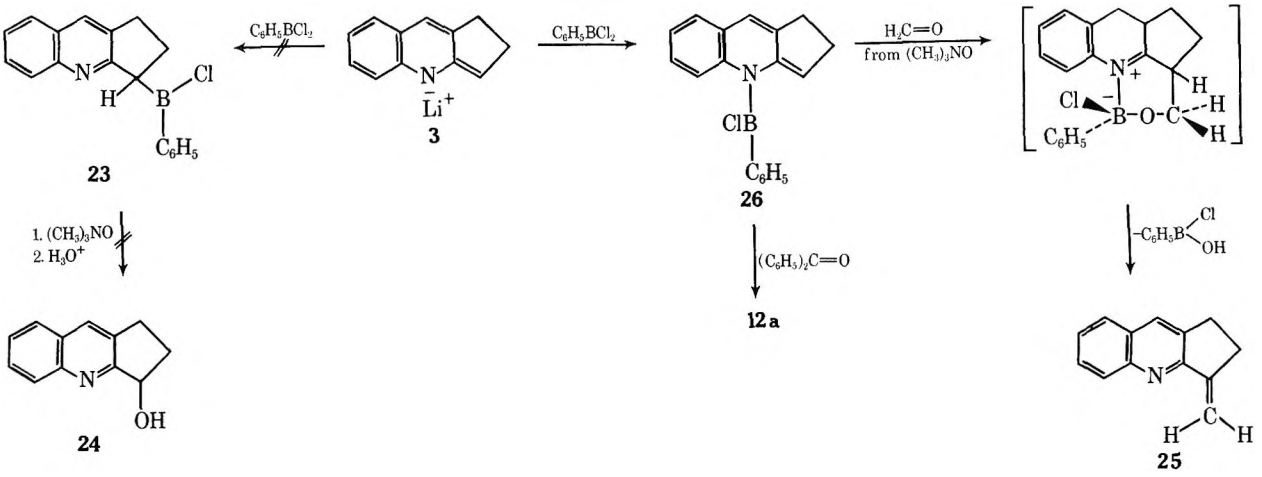
(7) G. Wittig and H. Wulff, *Proc. Robert A. Welch Found. Conf. Chem. Res., 9th, 1965*, 31, (1966).

(8) This reagent performs the quantitative oxidation of a wide variety of carbon–boron linkages and hence serves as an excellent diagnostic tool for such linkages. *Cf.* R. Köster and Y. Morita, *Justus Liebigs Ann. Chem.*, **704**, 70 (1967).

(9) E. Müller, Ed., "Houben-Weyls Methoden der Organischen Chemie," Band XI/2, Thieme Verlag Stuttgart, 1958, pp 191–193.

(10) Details of the general manipulative procedures and the instrumental methods are given in the previous article, ref 1.

SCHEME V



solution of 9-fluorenone (19.0 g, 100 mmol) in 200 ml of dry benzene. The mixture was stirred for 2 hr and hydrolyzed with a saturated aqueous solution of sodium bicarbonate, and the crude 2,3-dihydro-3-(9-hydroxy-9-fluorenyl)-1*H*-cyclopenta[*b*]quinoline (**11b**) was filtered off and washed with some hexane, 58.6 mmol (59%). Three recrystallizations from a chloroform–petroleum ether (bp 30–60°) pair afforded colorless crystals of an analytical sample of **11b**, mp 166.5–167.5°. Infrared spectral band at 2.95 μ (CH_2Cl_2).

Anal. Calcd for $C_{25}H_{19}NO$: C, 85.93; H, 5.48. Found: C, 85.72; H, 5.47.

C. With Phenylboron Dichloride, Followed by Trimethylamine Oxide in Benzene.—To a slurry of **3**, prepared from 25.0 mmol of **4**, was added a solution of 4.30 g (27.0 mmol) of phenylboron dichloride in 50 ml of dry benzene. The tan solution was stirred at room temperature for 20 hr and thereupon the ether was distilled off by the slow addition of more benzene during refluxing. To the refluxing and stirred reaction mixture was added 6.36 g (84.5 mmol) of anhydrous trimethylamine oxide in portions over a period of 45 min. During a further heating period of 100 min a nitrogen stream was used to sweep the liberated trimethylamine into a known amount of standard acid. Titration revealed that 1.5 equiv of $(CH_3)_3N$ or $(CH_3)_2NH$ had been liberated. Thereupon, 20 ml of methanol was added and the reaction mixture heated to reflux for 1 hr. The $(CH_3O)_3B$ and methanol were distilled off and the residue was hydrolyzed. The organic layer was extracted with 1 *N* hydrochloric acid, the acid extracts were separated and made basic, and the liberated amines were taken up in benzene. Separation of the organic layer, drying over anhydrous calcium sulfate, removal of solvent, and distillation under reduced pressure afforded a 71% recovery of **4** (melting point and ir). By examination of the amine fraction before distillation by tlc, the absence of cyclopenta[*b*]quinoline (**1a**) and 2,3-dihydro-3-hydroxy-1*H*-cyclopenta[*b*]quinoline (**24**) could be demonstrated.

D. With Phenylboron Dichloride, Followed by Trimethylamine Oxide in Toluene.—Exactly as in the preceding section, **3** was treated with the boron halide, but the ether–benzene was distilled off with the simultaneous addition of 175 ml of dry toluene. Also, a 6-hr reflux followed the addition of trimethylamine oxide. A total of 2.3 equiv of amine ($(CH_3)_3N$ or $(CH_3)_2NH$) was liberated. Usual work-up furnished an amine fraction (3.5 g) that by tlc contained neither **1a** nor **24**. Column chromatography on neutral alumina with a petroleum ether (bp 30–60°) eluent gave back **4** and 1.73 g (38.2%) of 2,3-dihydro-3-methylene-1*H*-cyclopenta[*b*]quinoline (**25**). An analytical sample was obtained by recrystallizations from petroleum ether as colorless flakes, mp 103–105°. Spectral data: ir λ_{max}^{Nujol} 6.25, 6.45 μ (arom conj C=CH_2); nmr (CCl_4) 2.88 (s, 4 H, CH_2CH_2), 5.20 (br s), and 6.21 (br s, C=CH_2), and 7.2–8.1 ppm (m, 5 H).

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.16; N, 7.73. Found: C, 85.80; H, 6.18; N, 7.74.

E. With Phenylboron Dichloride, Followed by Benzophenone.[11]—To a tan slurry of **3**, prepared from 100 mmol of **4**, according to the foregoing procedure, was added a solution of 7.94 g (50.0 mmol) of phenylboron dichloride in 50 ml of dry benzene. After a 5-hr stirring period a solution of benzophenone (18.2 g, 100 mmol) in 100 ml of benzene was added and the mixture refluxed 16 hr. Examination by tlc showed the presence of carbinol **11a** but definitely no benzhydrol. Distillative replacement of the benzene and ether by toluene, a 44-hr reflux period, and hydrolytic work-up gave crude, bright yellow 2,3-dihydro-3-diphenylmethylene-1*H*-cyclopenta[*b*]quinoline (**12a**), 11.3 g. Recrystallizations from 95% ethanol gave 9.3 g (28%), mp 161.5–162°. For spectral data, *cf.* section on **12a**.

Anal. Calcd for $C_{25}H_{19}N$: C, 89.87; H, 5.73. Found: C, 89.71; H, 5.63.

F. With Triphenylborane.—To a slurry of **3**, prepared from 25 mmol of **4**, was added a solution of triphenylborane[12] (6.05 g, 25 mmol) in 50 ml of dry benzene. The dark mixture was heated at the reflux temperature for 22 hr and then treated water at 0° (no gas evolution). The separated organic layer was extracted with dilute sodium hydroxide to remove any boron compounds, dried over anhydrous calcium sulfate, and heated *in vacuo* to remove the solvent. Column chromatography of the residue on neutral alumina and elution with petroleum ether permitted recovery of 3.33 g (79%) of **4**, as verified by melting point and ir spectrum. No **1a** was detected in any of the fractions.

The aqueous layer of the hydrolyzed reaction mixture was filtered and then treated with an aqueous solution of 2.67 g (28 mmol) of trimethylammonium chloride. A white solid which was thought to be principally trimethylammonium triphenylborohydride was deposited immediately, 1.8 g (21%). The colorless solid melted at *ca.* 120°, decomposing with gas evolution and resolidifying to a colorless material, mp 150–152° [$(C_6H_5)_3B$ lit.[12] mp 151–152°]. Solution in ethanol and addition of dilute hydrochloric acid gave an evolution of hydrogen. Its infrared spectrum in KBr showed broad bands between 4.0 and 5.6 μ (BH and HCr_3^+) and other bands at 6.8 (BC_6H_5) 13.5 and 14.2 μ (C_6H_5).

Reaction of 4 with Phenylmagnesium Bromide.—A solution of **4** (16.9 g, 100 mmol) in 100 ml of benzene and 100 mequiv of filtered[13] ethereal phenylmagnesium bromide was stirred for 14 hr at 25° and for 25 hr at reflux. A solution of benzophenone (19.2 g, 105 mmol) in 100 ml of dry benzene was added and the reaction mixture heated at reflux for 4 hr. After the usual hydrolytic work-up (*cf. supra* section B), isolation of the crude solid by filtration, and recrystallization, 16.1 g (46%) of pure 2,3-dihydro-α,α-diphenyl-1*H*-cyclopenta[*b*]quinoline-3-methanol (**11a**) was obtained, mp 153–155° (from methylene chloride). The organic filtrate from this isolation was freed of solvent to leave 20.6 g of dark yellow oil, which contained *ca.* 10% of **11a**, 30% of **4**, 20% of benzophenone, 10% of triphenylcarbinol, and 10% of benzhydrol (vpc and tlc).

Reactions of 11b with Phenylmagnesium Bromide and of 11b with Phenyllithium.—When a solution of **11b** (1.5 g, 4.3 mmol) in 50 ml of dry toluene was heated at reflux with 4.5 mequiv of ethereal phenylmagnesium bromide solution for 45 hr, tlc ex-

(11) This experiment was performed by Dr. Robert L. Harrell, Jr.

(12) G. Wittig and P. Raff, *Justus Liebigs Ann. Chem.*, **573**, 195 (1951).

(13) The Grignard reagent had to be filtered through a sintered glass frit to ensure the absence of magnesium particles, also being able to cause reduction.

amination showed that some reversal to 4 and 9-fluorenone had occurred but that no 9-fluorenol was formed.

Similar treatment of **11b** in toluene with ethereal phenyllithium solution caused the formation of **4** and benzophenone but not the formation of benzhydrol.

2,3-Dihydro-3-diphenylmethylene-1*H*-cyclopenta[*b*]quinoline (12a).—A solution of 13.5 g (38.6 mmol) of carbinol **11a** was dissolved in 200 ml of warm, glacial acetic acid and then 24 ml of concentrated sulfuric acid was added. The solution was brought to a boil for 5 min and then poured over ice. Further dilution with water gave 9.1 g of crude **12a**. After solution in 2 l. of hot ethanol, decolorizing with charcoal, filtering, and cooling, 7.47 g (55%) of fluffy yellow needles was obtained: mp 160–162°; ir λ_{max}^{KBr} 6.20 and 6.5 μ (arom conj C=C); nmr ($CDCl_3$) 3.04 (s, 4 H, CH_2CH_2), 7.3–7.85 ppm (m, 15 H); uv $\lambda_{max}^{95\% EtOH}$ 352 mμ (log ϵ 4.31) 282 (4.37), and 228 (4.62).

3-Diphenylmethylene-3*H*-cyclopenta[*b*]quinoline (13, 3-Diphenylmethylene-3*H*-Benzo[*b*][1]pyrindine).—A solution of **12a** (6.64 g, 20.0 mmol) in 200 ml of benzene was mixed at 25° with a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 4.56 g, 20.0 mmol) in 250 ml of benzene. The mixture was heated under reflux until (29 hr) tlc analysis showed the DDQ to have been consumed. The cooled mixture was diluted with petroleum ether to precipitate the quinol, DDQ·2H. (Before this considerable amounts of red-brown material had deposited on the walls of the reaction vessel.) The filtrate was treated with charcoal, refiltered, and then concentrated. The resulting reddish precipitate was collected and recrystallized from 95% ethanol. The golden-orange, flaky crystals of **13** melted at 153.5–155.5°, 2.05 g (31%). Spectral data: ir λ_{max}^{KBr} 6.30 and 6.40 μ (arom conj C=C); nmr (CCl_4) 6.87 (s, 2 H) and 7.3–7.8 ppm (m, 15 H); uv $\lambda_{max}^{95\% EtOH}$ 402 mμ (log ϵ 3.93), 307 (4.52), and 237 (4.51). The picrate was composed of red, feathery crystals, mp 151–155°.

Anal. Calcd for $C_{25}H_{17}N$: C, 90.60; H, 5.17; N, 4.23. Found: C, 90.50; H, 5.05; N, 4.41.

Attempted Dehydration of 2,3-Dihydro-3-(9-hydroxy-9-fluorenyl)-1*H*-cyclopenta[*b*]quinoline (11b).—When the dehydration of **11b** (6.86 g, 19.8 mmol) with 12 ml of concentrated sulfuric acid in 100 ml of glacial acetic acid was attempted in the manner successful for **11a**, no dehydration was achieved. Usual work-up yielded 94% of 9-fluorenone and 90% of **4** (melting point and infrared spectral identification). Even refluxing a solution of **11b** in benzene with a crystal of *p*-toluenesulfonic acid resulted only in cleavage into 9-fluorenone and **4**.

Lithium Salt of Benzo[*b*][1]pyrindine (2). A. With Benzophenone.—A solution of freshly distilled cyclopenta[*b*]quinoline (1.23 g, 7.38 mmol) in 50 ml of benzene was treated dropwise at 0° with 7.45 mequiv of ethereal phenyllithium solution. After 10 min a solution of benzophenone (1.48 g, 8.1 mmol) in 25 ml of benzene was added at 0° to the deep red solution. The dark purple mixture was stirred at room temperature for 12 hr and then hydrolyzed at 0°. Usual work-up gave 2.9 g of a dark yellow oil which was chromatographed on alumina by use of chloroform and ether eluents. The main fraction (2.2 g) was extracted with 6 *N* hydrochloric acid and these extracts were made basic to yield 0.5 g of a tan-colored solid, mp 220–225°, whose infrared resembled carbinol **11a**, band at 3.05 μ (OH). Because of its higher melting point, compared with that of **11a**, this is thought to have been a tautomer of the expected carbinol **20b**, namely the 3-hydroxydiphenylmethyl-1H derivative but a homogeneous sample could not be obtained.

The main chromatographic fraction, after the above-mentioned acid extraction, was freed of solvent and the residue was treated with picric acid dissolved in ethanol. The characteristic red picrate of **13** was isolated in 14% yield, as verified by melting point, mixture melting point, and spectral criteria. The mother liquors of the picric acid solution were freed of solvent and the solid was extracted with 5% sodium hydroxide. The residue consisted of 590 mg (40%) of benzophenone.

When lithium salt **2** was allowed to stand for 1 hr at 25° before the addition of the benzophenone, only a trace of **13** (tlc) was obtained in the subsequent reaction. By tlc the only other components were shown to be **1a** and benzophenone.

B. With Methyl Iodide.—To the deep red solution of **2**, prepared as above from 11.5 mmol of **1a** and 11.6 mequiv of phenyllithium, was added dropwise at 0° a solution of methyl iodide (0.77 ml, 12.3 mmol) in 20 ml of benzene. The reddish-purple solution was stirred for 15 min at 0° and 1 hr at 25°. The usual hydrolytic work-up was carried out promptly under a nitrogen atmosphere. The solvent was removed at <40° and the residue immediately distilled *in vacuo*. After a forerun of biphenyl (50 mg) the main fraction distilled at 112–116° (0.46 mm) as a pale-violet-colored oil, 0.80 g. The ir and nmr spectra of this sample (CCl_4) revealed it to be a mixture of monomethyl tautomeric (71%) and dimethyl derivatives (29%) of **1a**. Spectral data: ir λ_{max}^{neat} 2.9 (NH, almost undetectable in a 25% solution in CCl_4), 6.15 and 6.35 (arom conj C=C), 7.25 and 7.35 μ (internal $C(CH_3)_2$); nmr (CCl_4) 1.06 (d, J = 7 Hz, 1-CH_3-1H, 28%), 1.90 (d, J = 2 Hz, 1-CH_3-3H, 13%), 2.18 (br m, 3-CH_3-1H, 30%), 2.90 (br m, 3-CH_3-1-H), 3.26 (m, J = 2 Hz, and m, 1-$CHCH_3$ of 1-CH_3-1H and 3-CH_2 of 1-CH_3-3H), 1.22 (s, 1,1-$(CH_3)_2$-1H, 6%), and 1.32 ppm (s, 3,3-$(CH_3)_2$-3H, 23%); nmr spectrum unchanged after 220 hr.

Anal. Calcd for $C_{13}H_{11}N$: N, 7.73. Calcd for $C_{14}H_{13}N$: N, 7.17. Found: N, 7.73.

The assignment of signals was based upon the following considerations. (1) The doublet at 1.06 ppm arose from either the 1-CH_3-1H or 3-CH_3-CH isomer. In **1** and in **4** the 3-CH_2 lies at a lower field than the 1-CH_2. Since the methyl signal in the 3-CH_3 derivative of **4** occurs at 1.46 ppm, the methyl signal in the 3-CH_3-3H derivative of **1** would occur even lower. Hence, the observed doublet at 1.06 ppm fits the 1-CH_3-1H tautomer better. (2) The same reasoning leads to the assignment of the higher field doublet (1.90 ppm) to the 1-CH_3-3H tautomer and the lower field, broadened signal (2.18 ppm) to the 3-CH_3-1H tautomer. (3) Again, the sharpness of the signals and their chemical shifts prompted the assignments of the signals at 1.22 and 1.38 ppm to the 1,1-dimethyl-1H and to the 3,3-dimethyl-3H derivatives, respectively. (4) The peaks at 2.90 and at 3.26 ppm were confirmatory of the presence of the 3-CH_3-1H and 1-CH_3-1H tautomers, respectively. (5) Finally, the trends in chemical shifts assumed here are consistent with a recent nmr analysis of the methylindenes.[14]

Isomerization of 2,3-Dihydro-3-phenylmethylene-3*H*-cyclopenta[*b*]quinoline (12c).[15]—Under an atmosphere of nitrogen, a stirred, cooled solution of 1.28 g (5 mmol) of **27**[16] in 100 ml of dry tetrahydrofuran was admixed with 0.92 g (10 mmol) of potassium *tert*-butoxide. The reaction mixture promptly became intense violet in color. After a 3-hour stirring period at 0° the reaction mixture was treated with 100 ml of water. The organic product was extracted into ethyl ether, the ethereal extracts were dried over anhydrous calcium sulfate, and the solvent was removed to provide 1.10 g (86%) of crude 3-benzyl-1*H*-cyclopenta[*b*]quinoline (**28**), whose nmr spectrum showed the absence of significant amounts of any other tautomer. Recrystallization from 95% ethanol yielded colorless crystals, mp 72.5–73°. Spectral data: nmr ($CDCl_3$) 3.26 (m, 2 H), 4.10 (m, 2 H), 6.45 (m, 1 H), and 7.10–8.35 ppm (m, 10 H); mass spectrum (*m/e*, relative intensity, assignment) 257, 100, P; 180, 26, P − C_6H_5; 166, 15, P − $C_6H_5CH_2$; 127, 11, P − $C_3H_3(C_6H_5CH_2)$; 91, 30, $C_6H_5CH_2$.

Anal. Calcd for $C_{19}H_{15}N$: N, 5.44. Found: N, 5.61.

Registry No.—**2**, 31330-94-6; **3**, 31330-95-7; **4**, 5661-06-3; **5**, 31330-97-9; **11a**, 29520-62-5; **11b**, 31330-99-1; **12a**, 31331-00-7; **13**, 31331-01-8; **13** picrate, 31331-02-9; **15**, 31331-03-0; **16**, 31331-04-1; **17**, 31331-05-2; **18**, 31331-06-3; **19**, 31331-07-4; **25**, 30479-46-0; **28**, 31331-09-6; methyl iodide, 74-88-4; 9-fluorenone, 486-25-9; phenylboron dichloride, 873-51-8; phenylmagnesium bromide, 100-58-3.

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The Synthesis of 2,4-Diaryl-5*H*-indeno- and 2,4-Diaryl-5*H*-pyridocyclopenta[1,2-*d*]pyrimidin-5-ones

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A series of 2,4-diaryl-5*H*-indeno[1,2-*d*]pyrimidin-5-ones (**4a–f**) was prepared by condensing 2-(para-substituted benzylidene)-1,3-indandiones (**1a–f**) with benzamidine in the presence of sodium methoxide. The reaction of compound **4a** with hydrazine yielded the corresponding hydrazone **6**, the azine **7**, 2,4-diphenyl-5*H*-indeno[1,2-*d*]-pyrimidin-5-ol (**5a**), or 2,4-diphenyl-5*H*-indeno[1,2-*d*]pyrimidine (**8a**), depending upon the conditions. 6-(Para-substituted benzylidene)-5*H*-1-pyrindine-5,7(6*H*)-diones (**9a–e**) reacted with benzamidine to yield mixtures of two isomeric 2,4-diaryl-5*H*-pyridocyclopenta[1,2-*d*]pyrimidin-5-ones (**10a–e** and **11a–e**).

The condensation of 2-benzylidene-1,3-indandione (**1a**) with guanidine to form 2-amino-4-phenyl-5*H*-indeno[1,2-*d*]pyrimidin-5-one was reported by this laboratory.[1] Continuation of work on the cyclization reactions of **1a** led us to investigate the reaction of a number of 2-(para-substituted benzylidene)-1,3-indandiones (**1a–f**) and of their aza analogs, the 6-(para-substituted benzylidene)-5*H*-1-pyrindine-5,7-(6*H*)-diones (**9a–e**), with benzamidine (**2**).

The reaction of α,β-unsaturated ketones with benzamidine to form substituted pyrimidines has been reported by Dodson and Seyler in 1951.[2] Since then this synthesis has not been further explored.[3]

We found that when 2 equiv of the benzylidene-indandiones **1a–f** were allowed to react with 1 equiv of benzamidine in the presence of 4 equiv of sodium methoxide 2,4-diaryl-5*H*-indeno[1,2-*d*]pyrimidin-5-ones (**4a–f**) were formed in maximum yields of 32%. Evidence for the structures of compounds **4** is provided by elemental analyses, spectral data, and the formation of derivatives as described below.

A possible mechanism for the formation of the indenopyrimidinones **4** is shown in Scheme I. It consists of a Michael addition of **2** to the activated double bond of **1**, followed by ring closure, dehydration to dihydroindenopyrimidinone, and dehydrogenation to **4** by base-catalyzed air oxidation. The role played by the air in this step was not completely investigated. The Michael adduct **3** was isolated in 34% yield when equivalent amounts of **1a**, the hydrochloride of **2**, and sodium methoxide were heated at reflux for 1 hr. This adduct was then cyclized to **4a** by heating at reflux in methanol with sodium methoxide. In this step, beside the formation of **4a**, a reverse Michael reaction took place simultaneously regenerating **1a**. When acetic acid was used in place of sodium methoxide in the cyclization of **3**, none of compound **4a** was formed and only **1a** was isolated from the reaction mixture.

The diarylindenopyrimidinones **4** reacted with hydrazine to give compounds **5**, **6**, **7**, or **8** (Scheme II) depending upon the conditions. Addition of indenopyrimidinones (**4a** and **4c**) to ethanolic solutions of hydrazine containing catalytic amounts of acetic acid, followed by heating the mixtures at reflux for 10 hr gave the corresponding carbinol derivatives **5a** and **5b** in 70–80% yields. The structures of these compounds are supported by elemental analyses and ir and nmr spectra. The probable mechanism for the formation of the carbinols involves the oxidation of hydrazine to diimide,[4–6] which then reduces the carbonyl group.[7,8] This reaction mechanism is postulated to proceed through a cis addition by means of a cyclic transition state.[9,10]

Addition of acetic acid to a refluxing propanolic solution of indenopyrimidinone **4a** and hydrazine with continued refluxing for 1 hr gave the hydrazone **6** in 40% yield. Elemental analyses and spectral data support this structure. Tlc shows that the carbinol **5a** and the indenopyrimidine **8a** are also formed as by-products in this reaction. When the above mixture was heated at reflux for 3 days, instead of 1 hr, no hydrazone was found and the reaction proceeded to the formation of the indenopyrimidine **8a** (63% yield), which was identical with an authentic sample prepared from 2-benzylidene-1-indanone and benzamidine. This unusual reaction, in which the alkaline catalyst used in the Wolff–Kishner reduction is omitted, has been previously observed in a few cases.[11–13] It is believed, however, that this is the first reported instance of a cyclic carbonyl compound being reduced to a hydrocarbon by hydrazine at refluxing propanol temperature and in the presence of acetic acid.

In the presence of potassium hydroxide, indenopyrimidinone **4a** reacted with hydrazine to give in refluxing propanol azine **7** in 90% yield and in diethylene glycol at 200°, as in the standard Wolff–Kishner reduction, compound **8a** in 64% yield.

Several attempts have been made to prepare 2-methyl-4-phenyl-5*H*-indeno[1,2-*d*]pyrimidin-5-one from **1a** and acetamidine hydrochloride. The only product isolated was the Michael 1:1 adduct (40% yield), which by treatment with acidic or basic catalysts regenerated compound **1a** with evolution of ammonia.

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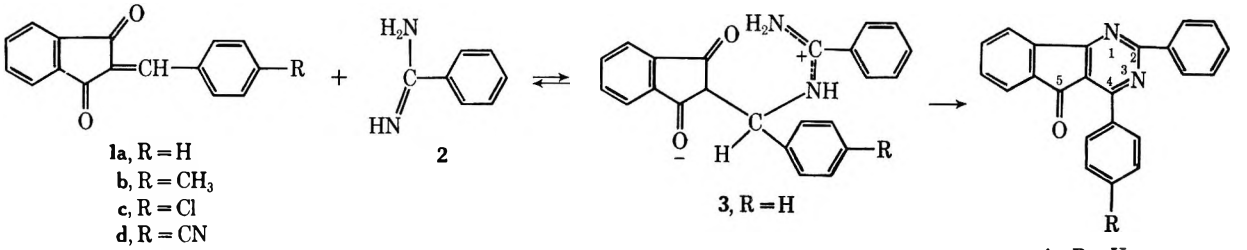
SCHEME I



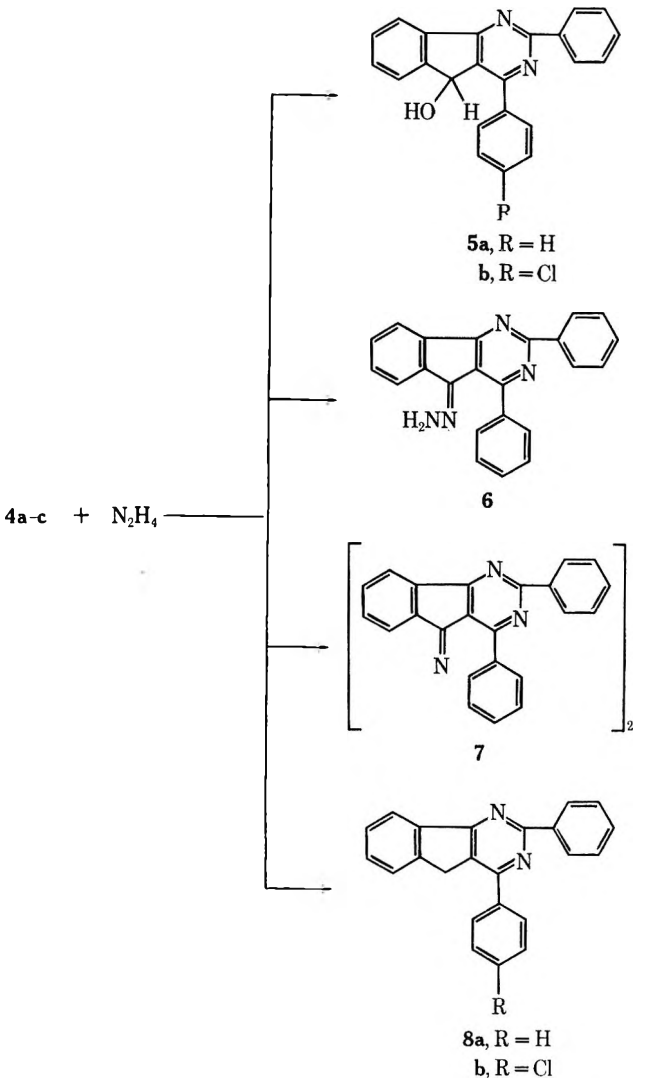
1a, R = H
b, R = CH_3
c, R = Cl
d, R = CN
e, R = OCH_3
f, R = $N(CH_3)_2$

2

3, R = H

4a, R = H
b, R = CH_3
c, R = Cl
d, R = CN
e, R = OCH_3
f, R = $N(CH_3)_2$

SCHEME II



5a, R = H
b, R = Cl

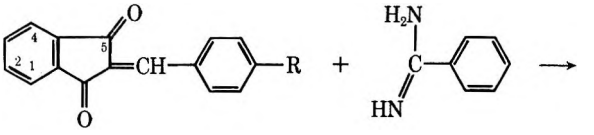
6

7

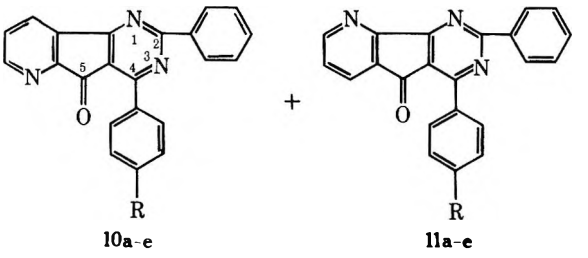
8a, R = H
b, R = Cl

The condensation of 6-(para-substituted benzylidene)-5*H*-1-pyrindine-5,7(6*H*)-diones (**9a–e**) with benzamidine in the presence of sodium methoxide, as in the method for preparing the indenopyrimidinones **4**, gave mixtures of the isomers **10** and **11** in 35% yield. Attempts to separate these two isomeric components were unsuccessful. The spectral properties of these mixtures were similar to those of compounds **4** and were in agreement with the assigned structures.

The substituted benzylidenepyrindinediones **9a–e** were prepared in very good yields from 6-(methoxycarbonyl)-5*H*-1-pyrindine-5,7-(6*H*)-dione and the appropriate aromatic aldehyde following the method developed by Neiland and Vanags for preparing compound **9a**.[14]



9a, R = H
b, R = CH_3
c, R = Cl
d, R = OCH_3
e, R = $N(CH_3)_2$



10a–e **11a–e**

Experimental Section[15]

2-(Para-substituted benzylidene)-1,3-indandiones (1a–f) were obtained in 80–98% yield by condensing 1,3-indandione with the appropriate aldehyde according to the procedure of Ionescu.[16] **2-(*p*-Cyanobenzylidene)-1,3-indandione (1d)** is not reported in the literature. It was obtained in 90% yield, from 1,3-indandione and *p*-cyanobenzaldehyde, as yellow needles: mp 232–233° (benzene); ir 2240–2230 (C≡N), 1735 and 1700 (C=O), 1640–1580 (C=C and C=N), and 847–738 cm^{-1} (aromatic bending).

Anal. Calcd for $C_{17}H_9NO_2$: C, 78.76; H, 3.48; N, 5.40. Found: C, 79.05; H, 3.48; N, 5.22.

2,4-Diaryl-5*H*-indeno[1,2-*d*]pyrimidin-5-ones (4a–f).—The following general procedure was used. To a stirred solution of sodium methoxide prepared from sodium (0.23 g, 0.01 g-atom) and anhydrous methanol (20 ml) were added benzamidine hydro-

(14) L. E. Neiland and G. Vanags, *Latv. PSR Zinat. Akad. Vestis*, **1**, 74 (1963); *Chem. Abstr.*, **60**, 4102*f* (1964).

(15) Melting points were taken on a Fisher-Johns melting point apparatus between circular cover plates and are corrected. The infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer as potassium bromide pellets. Ultraviolet spectra were taken on a Perkin-Elmer spectrophotometer Model 202, using chloroform as the solvent. Nuclear magnetic resonance spectra were obtained on a Varian Associates spectrometer, Model A-60A, deuterated chloroform, unless otherwise noted, being used as the solvent. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard. Elemental analyses were performed by the Micro Analysis, Inc., Marshallton, Del., and by the M-H-W Laboratories, Garden City, Mich.

(16) M. V. Ionescu, *Bull. Soc. Chim. Fr.*, **47**, 210 (1930).

TABLE I
2,4-DIARYL-5H-INDENO[1,2-d]PYRIMIDIN-5-ONES (4a–f)

Compd	R	Mp, °C[a]	Yield, %	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
4a	H	194–195	29	$C_{23}H_{14}N_2O$	82.67	82.83	4.19	4.34	8.38	8.44
4b	CH_3	218–220[b]	24	$C_{24}H_{16}N_2O$	82.76	82.83	4.60	4.70	8.05	7.92
4c	Cl	233–235	32	$C_{23}H_{13}ClN_2O$	74.90	74.82	3.53	3.51	7.60	7.51
4d	CN	272–274	6.6	$C_{24}H_{13}N_3O$	80.22	80.44	3.62	3.66	11.70	11.73
4e	OCH_3	204–205[b]	15	$C_{24}H_{16}N_2O_2$	79.12	79.16	4.40	4.23	7.69	7.38
4f	$N(CH_3)_2$	240–243[b]	26	$C_{25}H_{19}N_3O$	79.57	79.55	5.04	4.92	11.14	11.20

[a] Crystallization solvent, benzene–ethanol mixture. [b] Isolated by chromatography on alumina (benzene as eluent).

chloride dihydrate (0.48 g, 0.0025 mol) and the appropriate 2-(para-substituted benzylidene)-1,3-indandione (0.005 mol) at room temperature. The mixture was heated at reflux for 24 hr (ammonia evolution) and cooled overnight. The precipitate was collected, washed several times with methanol and with water, and dried to give compounds **4** as yellow needles.

The melting points, yields, and analytical data of compounds **4a–f** are listed in Table I. The ir spectra showed a single C=O band at 1750–1710 cm^{-1}, C=C and C=N absorptions at 1625–1530 cm^{-1}, consisting of several bands, and aromatic absorptions in the intervals of 760–755 and 690–683 cm^{-1}; in addition, bands at 2220–2210 cm^{-1} for compound **4d**, at 1235–1185 cm^{-1} for compound **4e**, and at 1365–1360 cm^{-1} for compound **4f**; uv λ_{max} at 250–260 mμ (ε 23,000–36,000) and 300–307 (34,000–44,000); nmr showed a singlet at 2.45 and an aromatic multiplet at 7.25–8.94 for compound **4b** and a singlet at 3.95 and an aromatic multiplet at 6.95–8.9 for compound **4e**, integration 3:13 for compounds **4b** and **4e**.

Hydrazone of 4a (6).—A mixture of **4a** (0.34 g, 0.001 mol), 1-propanol (30 ml), and 95% hydrazine (0.2 ml) was heated at reflux for 1 hr. Acetic acid (0.05 ml) was added, and the mixture was refluxed for an additional hour and then cooled in ice overnight. Filtration and washing of the cake with methanol and then with water gave 0.14 g (40%) of **6** as pale yellow crystals: mp 198–199° (ethanol); ir 3300 and 3200 (N—H), 1580–1530 (C=C and C=N) and 745–690 cm^{-1} (aromatic bending); nmr (DMSO-d_6) showed a singlet (broad) at 3.40 (2, NH) and an aromatic multiplet at 7.35–8.80 (14 protons).

Anal. Calcd for $C_{23}H_{16}N_4$: C, 79.31; H, 4.59; N, 16.10. Found: C, 79.59; H, 4.56; N, 15.95.

In an attempt to obtain additional hydrazone **6**, the reaction filtrate was evaporated to dryness under reduced pressure. The residue was found to be a mixture of compounds **4a**, **5a**, **6**, and **8a** by thin layer chromatography under uv.

The 2,4-dinitrophenylhydrazone of 4a was prepared by adding a solution consisting of 0.20 g (0.001 mol) of 2,4-dinitrophenylhydrazine, 1 ml of concentrated sulfuric acid, 1.5 ml of water, and 5 ml of ethanol to a solution of 0.25 g (0.75 mmol) of **4a** in 20 ml of a boiling 1:1 chloroform–ethanol mixture and continuing refluxing for 0.5 hr. A 76% yield of orange crystals, mp 275° dec, was obtained. The ir spectrum showed a characteristic nitro absorption in the interval 1550–1500 cm^{-1} and no carbonyl band.

Anal. Calcd for $C_{29}H_{18}N_6O_4$: C, 67.70; H, 3.50; N, 16.34. Found: C, 67.70; H, 3.35; N, 16.34.

The 2,4-dinitrophenylhydrazone of 4e was obtained by following the procedure above described for the dinitrophenylhydrazone of **4a**. Bright orange crystals, mp 300°, were obtained.

Anal. Calcd for $C_{30}H_{20}N_6O_5$: C, 66.18; H, 3.67. Found: C, 66.47; H, 3.69.

2-Benzylidene-1,3-indandione-Benzamidine 1:1 Adduct (3).—To a solution of sodium methoxide prepared from sodium (0.12 g, 0.005 g-atom) and anhydrous methanol (20 ml) were added 0.96 g (0.005 mol) of benzamidine hydrochloride dihydrate and 1.17 g (0.005 mol) of **1a** at room temperature. The mixture was refluxed for 1 hr and cooled in ice for 1 day. Filtration, washing, and drying gave 0.59 g (34%) of **3** as bright orange needles: mp 168° dec; insoluble in most organic solvents and slightly soluble in cold water; ir spectrum showed a strong and broad band at 3200–2900 cm^{-1} (>N^+H, =N^+H_2, and aromatic CH stretching vibrations),[17] and absorptions at 1680–1675 and 1550–1500 cm^{-1} (enolate anion vibrations).[18] The strong C=N^+ absorption in benzamidine hydrochloride[19] (1700–1675 cm^{-1}) was shifted to 1620–1600 cm^{-1} in compound **3**; nmr (DMSO-d_6) showed a singlet at 6.02 (assigned to the methine proton)[20] and an aromatic multiplet at 7.00–8.20 in the ratio 1:17. The amidinium protons were shown to be contained in the aromatic multiplet, since the ratio of the above signals was 1:14 after D_2O exchange. No enolic protons were observed.

Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.97; H, 5.08; N, 7.91. Found: 78.07; H, 5.08; N, 7.65.

Cyclization of 3.—To a solution of sodium methoxide prepared from sodium (0.023 g, 0.001 g-atom) and anhydrous methanol (10 ml) was added **3** (0.35 g, 0.001 mol) at room temperature. The mixture was refluxed for 24 hr (ammonia evolution) and cooled in ice overnight. The crude mixture recrystallized from a 1:1 ethanol–benzene mixture gave 0.07 g (30%) of **4a** as yellow crystals, mp 194–195°. Mixture melting point with a sample of **4a** prepared as above showed no depression.

Acidification of the reaction filtrate with 6 *N* hydrochloric acid and purification of the precipitate by fractional crystallization or column chromatography (chloroform–hexane mixture as eluent) resulted in the formation of **1a**, as shown by mixture melting point with an authentic sample.

2-Benzylidene-1,3-indandione-Acetamidine 1:1 Adduct.—It was prepared following the procedure above described for compound **3**, except that 0.48 g (0.005 mol) of acetamidine hydrochloride was used in place of benzamidine hydrochloride. A 40% yield of yellow orange needles, mp 181° dec, was obtained. The ir spectrum was similar to that of **3**; nmr (DMSO-d_6) showed a singlet at 2.20, a singlet at 5.68, and an aromatic multiplet at 6.90–7.60 in the ratio of 3:1:12, respectively. The amidinium protons were shown to be contained in the aromatic multiplet, since the ratio of the above signals after D_2O exchange was 3:1:9. No enolic protons were found.

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.97; H, 5.48; N, 9.59. Found: C, 73.85; H, 5.61; N, 9.52.

2,4-Diphenyl-5H-indeno[1,2-d]pyrimidin-5-ol (5a).—A hot solution of **4a** (0.34 g, 0.001 mol) in an anhydrous benzene–ethanol mixture (35 ml) was added dropwise to a stirred solution of 95% hydrazine (0.25 ml), anhydrous ethanol (5 ml), and glacial acetic acid (0.025 ml). The reaction mixture was heated at reflux for 10 hr and then evaporated to dryness under reduced pressure. The residue was washed with methanol and with water and dried to give 0.28 g (83%) of **5a** as pale yellow crystals: mp 259–261° (methanol–benzene); ir 3200–3150 (OH), 1575–1545 (C=C and C=N), 1040 (CO stretching), and 750, 690 cm^{-1} (aromatic bending); nmr (DMSO-d_6) showed a singlet at 3.42 (1, OH), a singlet at 6.05 (1, CH), and an aromatic multiplet at 7.0–8.9 (14 protons). The position of the hydroxyl proton was determined by D_2O exchange.

Anal. Calcd for $C_{23}H_{16}N_2O$: C, 82.13; H, 4.76; N, 8.33. Found: C, 82.11; H, 4.81; N, 8.36.

4-(p-Chlorophenyl)-2-phenyl-5H-indeno[1,2-d]pyrimidin-5-ol (5b).—A suspension of 0.37 g (0.001 mol) of **4c**, 20 ml of anhydrous ethanol, 1 ml of 95% hydrazine, and 0.05 ml of acetic acid, prepared as for compound **5a**, was heated at reflux for 10 hr and then cooled in ice for several hours. The precipitate was collected, washed with methanol and water, and dried to give 0.26 g (70%) of **5b** as pale yellow crystals, mp 257–259° (ethanol). The ir and nmr spectra were similar to those of compound **5a**.

Anal. Calcd for $C_{23}H_{15}ClN_2O$: C, 74.45; H, 4.05; N, 7.56. Found: C, 74.57; H, 4.01; N, 7.47.

(17) J. C. Grivas and A. Tawrins, *Can. J. Chem.*, **37**, 1260 (1959), and Sadtler Standard Spectra, IR 18879 (1961).

(18) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1964.

(19) Sadtler Standard Spectra, IR 18879 (1961).

(20) C. L. Stevens, R. C. Freeman, and K. Noll, *J. Org. Chem.*, **30**, 3719 (1965).

TABLE II

6-(PARA-SUBSTITUTED BENZYLIDENE)-5*H*-1-PYRINDINE-5,7-(6*H*)-DIONES (9a–e)

Compd	R	Mp, °C[a]	Yield, %	Formula	% C		% H		% N	
					Calcd	Found	Calcd	Found	Calcd	Found
9a	H	175–176[b]	68	$C_{15}H_9NO_2$	76.60	76.48	3.83	3.88	5.96	5.98
9b	CH_3	222–223	70	$C_{16}H_{11}NO_2$	77.11	77.05	4.42	4.54	5.62	5.42
9c	Cl	241–242	83	$C_{15}H_8ClNO_2$	66.77	66.73	2.97	2.99	5.19	5.12
9d	OCH_3	204–205	87	$C_{16}H_{11}NO_3$	72.45	72.68	4.15	4.38	5.28	5.18
9e	$N(CH_3)_2$	240–242	95	$C_{17}H_{14}N_2O_2$	73.38	72.99	5.04	5.12	10.07	9.91

[a] Recrystallization solvent, dioxane or dioxane–water mixture. [b] Reference 12.

TABLE III

MIXED 2,4-DIARYL-5*H*-PYRIDOCYCLOPENTA[1,2-*d*]PYRIMIDIN-5-ONES (10a–e + 11a–e)

Compd	R	Mp, °C	Yield, %	Formula	% C		% H		% N	
					Calcd	Found	Calcd	Found	Calcd	Found
10a + 11a	H	225–236	36	$C_{22}H_{13}N_3O$	78.80	78.52	3.88	3.97	12.53	12.33
10b + 11b	CH_3	234–246	35	$C_{23}H_{15}N_3O$	79.08	79.04	4.30	4.30	12.04	11.95
10c + 11c	Cl	260–275	38	$C_{22}H_{12}ClN_3O$	71.69	71.69	3.25	3.57	11.37	11.51
10d + 11d	OCH_3	220–232	34	$C_{23}H_{15}N_3O_2$	75.62	75.67	4.11	4.29	11.50	11.27
10e + 11e	$N(CH_3)_2$	272–288	37	$C_{24}H_{18}N_4O$	76.19	76.46	4.76	4.65	14.82	14.85

2,4-Diphenyl-5*H*-indeno[1,2-*d*]pyrimidin-5-one Azine (7).—A mixture of **4a** (0.34 g, 0.001 mol), 1-propanol (30 ml), 95% hydrazine (0.2 ml), and potassium hydroxide (0.056 g, 0.001 mol) was refluxed for 2.5 hr and then cooled in ice for several hours. The orange brown solid was collected by filtration and washed with water and with methanol to give 0.29 g (90%) of **7**: mp 300°; ir 1580–1540 (C=C and C=N absorption), 750 and 690 cm^{-1} (aromatic bending).

Anal. Calcd for $C_{46}H_{28}N_6$: C, 83.13; H, 4.22; N, 12.65. Found: C, 83.00; H, 4.31; N, 12.55.

2,4-Diphenyl-5*H*-indeno[1,2-*d*]pyrimidine (8a). A. From 2-Benzylidene-1-indanone.—It was obtained by the procedure above described for preparing compound **4a**, except that 2-benzylidene-1-indanone[21] (1.1 g, 0.005 mol) was used in place of 2-benzylidene-1,3-indandione. The crude product was dissolved in chloroform, and the solution was mixed with activated alumina and evaporated to dryness. Chromatography of the residue over an alumina packed column (elution with benzene) gave 0.19 g (23%) of **8a** as colorless needles: mp 187–189° (ethanol); ir 1600–1540 (C=C and C=N absorptions) and 750–690 cm^{-1} (aromatic bending); nmr showed a singlet at 3.93 (2, CH_2) and an aromatic multiplet at 7.36–8.94 (14 protons). The position of the methylene protons was the same as that found in 2-benzylidene-1-indandone (δ 3.90).

Anal. Calcd for $C_{23}H_{16}N_2$: C, 86.25; H, 5.00; N, 8.75. Found: C, 86.39; H, 5.27; N, 8.39.

2,4-Diphenyl-5*H*-indeno[1,2-*d*]pyrimidine (8a). B. From Compound 4a.—A mixture of **4a** (0.96 g, 0.003 mol), 95% hydrazine (0.48 ml, 0.015 mol), potassium hydroxide (1.0 g, 0.018 mol), and diethylene glycol (15 ml) was heated (oil bath) to 120° and maintained for 1 hr. The condenser was removed and the mixture was heated to 200° and maintained at this temperature for 3 hr. The cooled solution was added to ice-cold water (150 ml). The precipitate was collected, dried, and chromatographed on alumina (elution with benzene) to give 0.61 g (64%) of **8a** as cream-colored crystals, mp 185–187° (ethanol), identical (mixture melting point and spectra) with compound **8a** prepared as described under A.

This compound was also obtained by heating at reflux for 1 hr a mixture of **4a** (0.34 g, 0.001 mol), 1-propanol (30 ml), and 95% hydrazine (0.2 ml), adding acetic acid (0.05 ml), refluxing for 3 days, and cooling overnight. The precipitate was collected, washed with methanol and then with water, and dried to give 0.21 g (63%) of **8a**. Mixture melting point with a sample of **8a**, prepared as described above, showed no depression.

2-Phenyl-4-(*p*-tolyl)-5*H*-indeno[1,2-*d*]pyrimidine (8b).—It was prepared following the procedure B described above for **8a**, except that compound **4b** (1.05 g, 0.003 mol) was used in place of **4a**. Chromatography gave 0.65 g (65%) of **8b** as cream-colored crystals, mp 185–187°.

(21) A. Hassner and N. H. Cromwell, *J. Amer. Chem. Soc.*, **80**, 893 (1958).

Anal. Calcd for $C_{24}H_{18}N_2$: C, 86.23; H, 5.39; N, 8.38. Found: C, 86.24; H, 5.44; N, 8.28.

6-(Para-substituted benzylidene)-5*H*-1-pyrindine-5,7-(6*H*)-diones (9a–e).—These compounds were prepared from 6-(methoxycarbonyl)-5*H*-1-pyrindine-5,7(6*H*)-dione and the appropriate aldehyde by following the procedure described by Neiland and Vanags for the preparation of compound **9a**.[12] The melting points, yields, and analytical data of compounds **9b–e** together with those of **9a** are listed in Table II. The ir spectra showed two bands at 1750–1720 and at 1700–1690 cm^{-1} (C=O), bands at 1610–1540 cm^{-1} (C=C and C=N), and aromatic bendings at 768–755 cm^{-1}. Compound **9d** showed bands also at 1266 and 1195 cm^{-1} and compound **9e** at 1380 cm^{-1}.

Mixed 2,4-Diaryl-5*H*-pyrido[2′,3′:4,5]cyclopenta[1,2-*d*]-pyrimidin-5-ones [10a–e] and 2,4-Diaryl-5*H*-pyrido[2′,3′:5,4]-cyclopenta[1,2-*d*]pyrimidin-5-ones (11a–e).—These mixtures were obtained by reacting compounds **9** with benzamidine according to the procedure above described for preparing compounds **4**. The crystallized products (benzene–ethanol mixtures) had broad melting points. Tlc showed the presence of two components, which could not be separated by fractional crystallization from benzene or ethanol or by column chromatography. The melting points, yields, and analytical data of these mixtures are listed in Table III. The ir spectra showed a single C=O band in the 1730–1710-cm^{-1} region, C=C and C=N absorptions at 1600–1500 cm^{-1}, consisting of several strong bands, and aromatic absorptions at 776–760 and 690–685 cm^{-1}; uv λ_{max} 242–249 mμ (ϵ 22,000–31,000) and 295–308 (26,000–32,000); nmr showed a singlet at 2.45 and an aromatic multiplet at 7.3–9.05 (integration 3:12) for mixture **10b** and **11b** and a singlet at 3.94 and an aromatic multiplet at 7.02–9.08 (integration 3:12) for mixtures **10d** and **11d**.

Registry No.—**1d**, 31316-87-7; **3**, 31570-93-1; **4a**, 31570-63-5; **4a** 2,4-DNPH, 31570-64-6; **4b**, 31570-65-7; **4c**, 31570-66-8; **4d**, 31570-67-9; **4e**, 31570-68-0; **4e** 2,4-DNPH, 31570-69-1; **4f**, 31570-70-4; **5a**, 31570-71-5; **5b**, 31570-72-6; **6**, 31570-73-7; **7**, 31570-74-8; **8a**, 31570-75-9; **8b**, 31570-76-0; **9a**, 31570-77-1; **9b**, 31570-78-2; **9c**, 31570-79-3; **9d**, 31570-80-6; **9e**, 31570-81-7; **10a**, 31570-82-8; **10b**, 31570-83-9; **10c**, 31570-84-0; **10d**, 31570-85-1; **10e**, 31570-86-2; **11a**, 31570-87-3; **11b**, 31570-88-4; **11c**, 31570-89-5; **11d**, 31570-90-8; **11e**, 31570-91-9; 2-benzylidene-1,3-indandione-acetamidine 1:1 adduct, 31570-92-0.

Acknowledgment.—We gratefully acknowledge the valuable assistance of Dr. Mario F. Sartori in connection with this research.

Nucleophilic Vinylic Substitution. I. The Synthesis and Reactions of 2-Substituted 3,3-Dichloroacrylonitriles

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Received April 2, 1971

Five 2-substituted 3,3-dichloroacrylonitriles (1 = 2-hydro, 2 = 2-chloro, 3 = 2-methyl, 4 = 2-cyano, and 5 = 2-phenyl) have been prepared and their reactions with methoxide and thiophenoxide studied. Spectral data and chemical reactivity indicate that 1–4 are coplanar molecules, whereas the phenyl group in 5 cannot lie in the same plane as the acrylonitrile system and does not activate the β-chlorine atoms. Nitrile 4 reacted exothermically with methanol to yield 3,3-dimethoxy-2-cyanoacrylimidyl chloride which hydrolyzed readily to the corresponding acrylamide. Nitriles 1, 2, 3, and 5 required the methoxide or thiophenoxide ion to substitute the vinylic chlorine atoms. Dichloromethylenetriphenylphosphorane, prepared from carbon tetrachloride and triphenylphosphorine, reacted with benzoyl cyanide to afford a 73% yield of nitrile 5.

With the exception of a few reports[1] the literature on nucleophilic substitution of activated vinylic chlorine atoms has dealt with systems which possessed only one activated halogen atom.[2]

A previous study on the cis and trans isomers of 3-chloroacrylonitrile showed that nucleophilic substitution of the vinyl halide proceeded in a straightforward manner.[3] Unfortunately, the literature on the substitution of two β-chlorine atoms from acrylonitriles is less clear. For example, Miller and Kalnins[1c] have reported that the reaction of 1 or 2,3-dichloroacrylonitrile with sodium *p*-toluenesulfinate resulted in shortening the acrylonitrile by one carbon to give *p*-toluenesulfonylacetonitrile. Others[1b] have reported that 2 reacted with sodium ethoxide in ethanol under all conditions to give only 3,3,3-triethoxy-2-chloropropionitrile. A more recent report showed that alkoxide reactions with 1 gave either ketene acetals or ortho esters depending upon the alkoxide/nitrile ratio.[1e] In this study we have found that the products from the reaction of substituted 3,3-dichloroacrylonitriles with methoxide or thiophenoxide depend on the molar ratio of the reactants and on the α substituent. The following nitriles were used in this study: 3,3-dichloroacrylonitrile (1), 2,3,3-trichloroacrylonitrile (2), 3,3-dichloro-2-methylacrylonitrile (3), 3,3-dichloro-2-cyanoacrylonitrile (4), and 3,3-dichloro-2-phenylacrylonitrile (5).

Preparation of the simplest member of this series (1) was first reported by Miller and Kalnins[1c] by the reaction of 2-acetoxy-3,3,3-trichloropropionitrile with zinc. More recently, 1 has been prepared in a 60% yield by the copyrolysis of carbon tetrachloride and acetonitrile.[1e] The procedure which we employed is outlined in Scheme I. The first three steps are similar to a procedure developed by Nesmeyanov[4] but avoids isolation of the intermediates. The oxime of 7 was obtained in a near-quantitative yield but underwent decomposition at room temperatures. Similarly unstable oximes have been reported for β-chlorovinyl aldehydes[5a] and an explosive decomposition was recorded during the distillation of 2-methylacrolein oxime.[5b] We found that mixing the oxime with an excess of cold acetic anhydride for at least 24 hr prior to distillation afforded a smooth dehydration to the nitrile.

2,3,3-Trichloroacrylonitrile (2) was prepared according to the procedure of Boeseken and Du Jardin;[6] however, by using a modification[7] for the hydrolysis of the trichloromethyl group, we were able to obtain 2 in a 59% yield starting from hexachloropropene.

3,3-Dichloro-2-methylacrylonitrile (3) has not been reported previously; however, it seemed reasonable to assume that the unknown 3,3-dichloro-2-methylacrylic acid (10) would be the most logical precursor (Scheme II). Morris and Kundiger[8] had previously shown that 3,3-dichloro-2-methylallyl alcohol (9) was unusually resistant to oxidation and required cold concentrated nitric acid or preferably hot chromic acid to convert 9 to the aldehyde 11. We have made a number of attempts to oxidize 9 to 10 using chromic acid or nitric acid under more severe conditions but without success. The only extractable material obtained from these reactions was varying amounts of 11 and small amounts of the very stable acetal 3,3-bis(3,3-dichloro-2-methyl-2-propenoxy)-1,1-dichloro-2-methyl-1-propene. Carbon dioxide was usually eliminated from these reactions indicating a surprisingly facile decarboxylation of the acid 10. A reinvestigation of the oxidation of 9 to 11 has revealed that dilute nitric acid containing vanadium pentoxide affords a more convenient synthesis and a slightly higher yield of 11.

The oxime of 11 was a stable white solid and was readily dried over phosphorus pentoxide without any noticeable decomposition. Dehydration of 12 with acetic anhydride proceeded quite smoothly giving 3 in 71% yield.

During one preparation of 12 the reaction mixture was heated and a stable yellow oil was obtained which has been identified as *O*-(3,3-dichloro-2-methyl-1-methoxyallyl)-3,3-dichloro-2-methylacrolein oxime (13). The appearance of three medium intensity bands in the 1600-cm^{-1} region, as well as a strong band at 914 cm^{-1} and shoulder at 880 cm^{-1}, strongly suggested the existence of a conjugated C=N and C=CCl_2 system and a nonconjugated C=CCl_2 group. The nmr spectrum consisted of five singlets with an integrated ratio

(1) For leading references, see (a) R. L. Soulen, D. G. Kundiger, S. Searles, Jr., and R. A. Sanchez, *J. Org. Chem.*, **32**, 2661 (1967); (b) A. Roedig, K. Grohe, and W. Mayer, *Chem. Ber.*, **100**, 2946 (1967); (c) B. Miller and M. V. Kalnins, *Tetrahedron*, **23**, 1145 (1967); (d) A. S. Gudkova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1248 (1962); (e) N. Hashimoto, Y. Kawano, and K. Morita, *J. Org. Chem.*, **35**, 828 (1970).

(2) Z. Rappoport, *Advan. Phys. Org. Chem.*, **7**, 1–114 (1969).

(3) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).

(4) A. N. Nesmeyanov, R. Kh. Freidlina, and L. I. Zakharkin, *Dokl. Akad. Nauk SSSR*, **99**, 781 (1954).

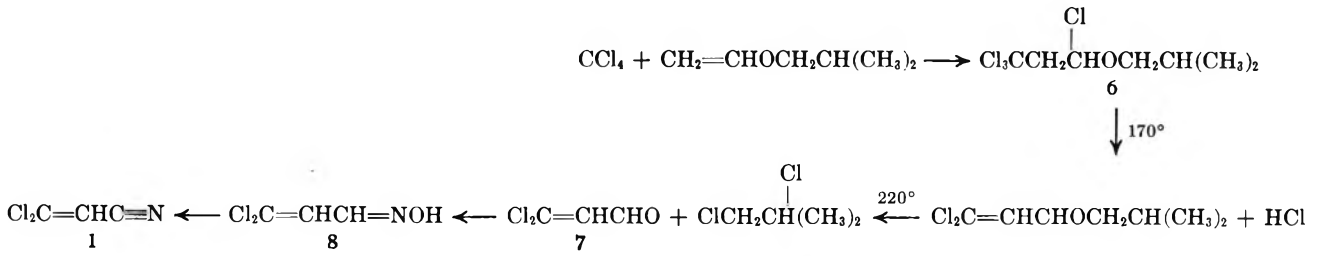
(5) (a) W. R. Benson and A. E. Pohland, *J. Org. Chem.*, **30**, 1126 (1965); (b) D. T. Mowry and R. R. Morner, *J. Amer. Chem. Soc.*, **69**, 1831 (1947).

(6) J. Boeseken and P. Du Jardin, *Recl. Trav. Chim. Pays-Bas*, **32**, 97 (1913).

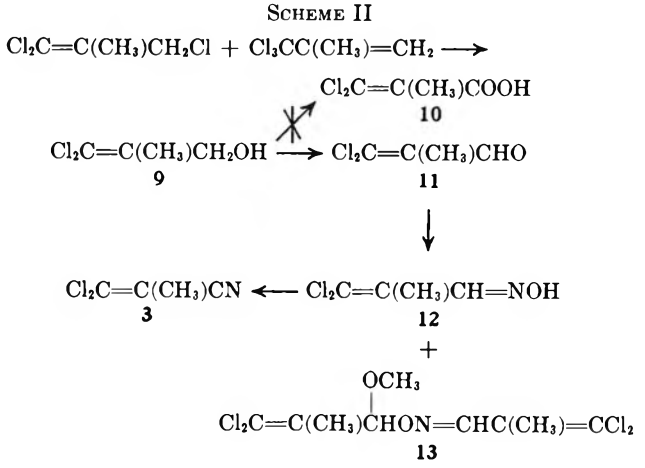
(7) F. Bergmann and L. Haskelberg, *J. Amer. Chem. Soc.*, **63**, 1437 (1941).

(8) D. G. Kundiger and G. F. Morris, *ibid.*, **80**, 5988 (1958).

Scheme I



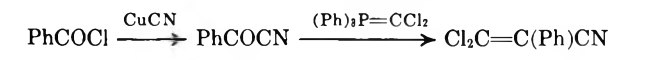
Scheme II



of 3:3:3:1:1. Two of the methyl proton absorptions appeared at δ 1.90 and 2.00 corresponding to the nonconjugated and conjugated C=CCH$_3$ group. The OCH$_3$ absorption at δ 3.48, the CH=N absorption at δ 8.20, and the OCHO absorption at δ 5.93 fell well within the acceptable ranges for these proton absorptions.[9] This appears to be the first example of an acetal which employed an oxime as one of the alcohol groups.

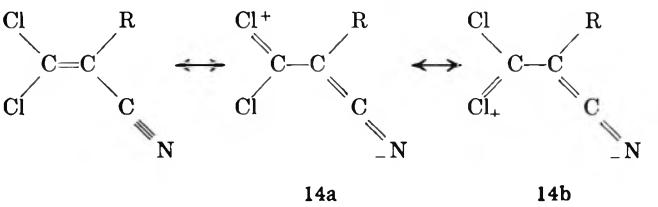
We have used the method developed by Josey, *et al.*,[10] to prepare 3,3-dichloro-2-cyanoacrylonitrile (**4**) and would urge that special care be taken in working with this compound as it is a powerful irritant to the throat and lungs.

Previously unreported 3,3-dichloro-2-phenylacrylonitrile (**5**) was readily obtained in two steps from ben-



zoyl chloride. The first step is well known[11] and proceeds in good yields. The Wittig reagent employed in the second step was prepared by the direct reaction of triphenylphosphine and carbon tetrachloride at room temperature. Since most acyl cyanides are thermally unstable and decompose rapidly in basic media, this method appears to be ideally suited for the preparation of simple α alkyl and aryl acrylonitriles.

Spectra.—The infrared and ultraviolet spectra of the five 3,3-dichloroacrylonitriles used in this study are tabulated in Table I. As expected, the C≡N and C=C frequencies have been shifted to the longer wavelengths indicating good conjugation and coplanarity of the π electrons. The *gem*-dichlorovinyl stretching frequency appeared as a strong absorption in the 920–975-cm^{-1} region well above the region 900–930-cm^{-1} suggested for nonconjugated dichlorovinyl absorption.[12] This rise in frequency is most likely due to a strengthening of the Cl–C bond due to election delocalization out of the β-chlorine atoms giving rise to resonance forms **14a** and **14b**.



14a **14b**

In a comparison of these chlorinated acrylonitriles with their corresponding hydrocarbon analogs it is apparent that the two β-chlorine atoms have very little if any effect on the nitrile absorption position. The α substituent, on the other hand, has a much more pronounced effect and exerted a shift of approximately 20 cm^{-1} in passing from electron-donating to electron-withdrawing groups. This is twice the shift apparent in various para-substituted benzonitriles[13] and suggests that the nature of the α substituent and not the β-halogen atom will be a controlling factor in chemical reactivity. Kinetic data supports this contention quantitatively.[14]

The nitrile absorption in **2** appeared as a weak doublet of nearly equal intensity at 2240 and 2213 cm^{-1}. This doublet is likely the result of Fermi resonance with an overtone of a strong band appearing at approximately 1115 cm^{-1}. Similar splitting of the nitrile absorption by Fermi resonance has been reported by Evans and Lo[15] for acetonitrile complexes of zinc.

Replacing the two β-chlorine atoms in **1**–**4** by CH$_3$O or PhS groups increased the intensity of the nitrile absorption and lowered the position of this band to the 2220- and 2205-cm^{-1} region. By contrast the nitrile absorptions in the ortho esters **17a**, **17b**, and **17c** and methyl phenylcyanoacetate appeared as a very weak absorption in the 2240–2250-cm^{-1} region.

The most notable feature of the C=C stretching frequency was the pronounced bathochromic shift caused by the PhS group. Compared with the C=C band position in the hydrocarbon analogs of **1**, **2**, and **3** (1621, 1607 and 1624 cm^{-1}, respectively), two β PhS groups lowered this band approximately 90 cm^{-1}. Recent evidence from esr studies strongly suggests that

(9) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 163–192.

(10) A. D. Josey, C. L. Dickinson, K. C. Dewhirst, and B. C. McKusick, *J. Org. Chem.*, **32**, 1941 (1967).

(11) E. C. Horning, "Organic Syntheses," Collect Vol. III, Wiley, New York, N. Y., 1955, p 112.

(12) A. Fujino, Y. Nagata, and T. Sakan, *Bull. Chem. Soc., Jap.*, **38**, 295 (1965).

(13) L. J. Bellany, "Advances in Infrared Group Frequencies," Methuen and Co. Ltd., Great Britain, 1968, p 72.

(14) Unpublished work.

(15) J. C. Evans and G. Y.-S. Lo, *Spectrochim. Acta*, **21**, 1033 (1965).

TABLE I

IR AND UV SPECTRA OF SUBSTITUTED 3,3-DICHLOROACRYLONITRILES

Compd	Ir, cm⁻¹ [a] CN	C=C	CCl_2	Uv [b] λ_{max}, nm	ϵ_{max}
Cl_2C=CHCN (1)	2232	1582	923	227.5	10,060
Cl_2C=CClCN (2)	2240, 2213	1562	952	238.5	10,820
Cl_2C=C(CH_3)CN (3)	2225	1596	937	228	11,960
Cl_2C=C($CN)_2$ (4)	2240	1549	975	243[c]	11,270[c]
Cl_2C=C(Ph)CN (5)	2220	1560[d]	928	226	9,410
				269	9,840
H_2C=CHCN	2231[e]	1621[e]		203[f]	6,100[f]

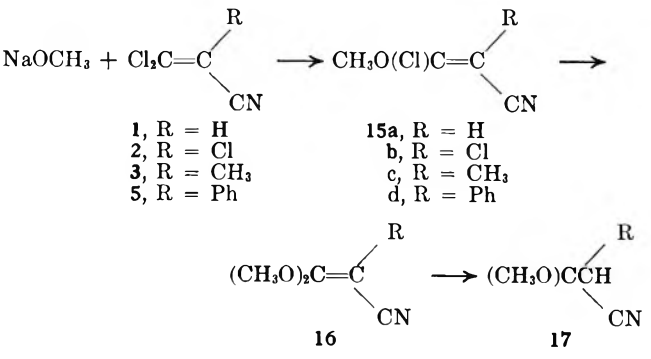
[a] Spectra were determined on neat liquid films except 4 which was run as a KBr pellet. [b] All spectra were obtained in 95% ethanol solvent. [c] Spectrum was started 3 min after addition of ethanol to nitrile 4. After 15 min the spectrum changed to λ_{max} 241 nm (ϵ 12,390). [d] The C=C stretching band and an aromatic absorption band overlapped in this band. [e] R. Heilmann and J. Bonnier, *C. R. Acad. Sci.*, **248**, 2595 (1959). [f] R. Heilmann, J. Bonnier, and G. de Gaudemaris, *ibid.*, **244**, 1787 (1957).

electronic factors due to the PhS group are not a result of electron donation,[16] but electron withdrawal through $d\pi$–$p\pi$ bonding of sulfur and the phenyl ring.[17] Chemical evidence given below also support this view.

The role of the β-chlorine atoms in promoting resonance delocalization in the acrylonitrile system was also apparent from the uv spectra. A measured bathochromic shift of about 12 nm per β chlorine compared favorably with the value 15 nm per β chlorine found in β,β-dichlorovinyl ketones.[18] In contrast to the latter system, however, it was apparent from the extinction coefficients that nitriles **1**–**4** suffered no loss of coplanarity when the α substituent was increased in size from hydrogen to a methyl group. Some distortion and loss of conjugation must occur in nitrile **5** since the extinction coefficient and chemical reactivity were unusually low for a molecule which had two "activating" groups. Inspection of molecular models indicates that the minimum angle between the phenyl group and the double bond is about 45°. A closer approach to coplanarity is prevented by the ortho hydrogens and the β-chlorine atom. Crystallographic data on 2-bromo-1,1-di-*p*-tolylethylene show that the cis phenyl ring is distorted by 55°.[19]

Reactions with Methoxide.—The reaction of methoxide ion with acrylonitriles **1**, **2**, **3**, and **5** proceeded through three clearly defined steps depicted in Scheme III. Each step of the reaction was quite rapid and

SCHEME III



required anhydrous conditions to avoid hydrolysis of **15**, **16**, or **17** to the methyl cyanoacetates.

The mechanism for nucleophilic substitution of activated vinylic halides is generally accepted to be an "addition-elimination" type involving a stabilized carbanion intermediate.[2] Systems possessing only one β halogen have been shown to generally yield products which retained the configuration of the starting material. We are presently investigating the structure of monosubstituted products **15** as there exists some controversy in the literature as to whether the initial product has the incoming nucleophile cis,[1d] trans,[20a] or a mixture of isomers.[20b]

The monomethoxy **15** and dimethoxy **16** products were best prepared by very slowly adding methanolic sodium methoxide to a dilute solution of the acrylonitrile until the desired product reached maximum yield as indicated by vpc analysis. Nevertheless, ketene acetals **16** were produced in some of the reaction mixtures long before the CH_3O/acrylonitrile ratios reached one. Ortho esters did not appear in appreciable quantities, however, until this ratio was greater than two (Table II).

TABLE II[a]

REACTION OF SODIUM METHOXIDE WITH 2-SUBSTITUTED 3,3-DICHLOROACRYLONITRILES

Acrylonitrile	Ratio, MeO/CN	Product[b]	Bp (mm) or mp, °C	$n^{25}D$	Yield, %
1	1.15	15a	32.5–33[c]		
2	0.94	15b[d]	28–30[c]		60[e]
1	2.00	16a	61–62 (0.1), 38–39[f]		94
2	1.90	16b	124 (25)	1.4588	78
3	1.90	16c	46–48 (0.8)	1.4523	82
1	2.10	17a	*c*, *g*	1.4235	38
2	2.10	17b	65–57 (1.0)	1.4386	20
3	2.20	17c	*c*	1.4262	60[e]
4	1.90	*h*	*c*	1.5596	67

[a] Satisfactory analytical values (±0.4% for C, H, and N) were reported for all compounds except **15b** (calcd: C, 30.6; Cl, 46.6. Found: C, 31.33; Cl, 44.7) and **17c** (Calcd: C, 52.81. Found: C, 53.39). Satisfactory Cl analyses were reported for **15a**, **16b**, and **17b**: Ed. [b] **15** = monomethoxy, **16** = ketene acetal, **17** = ortho ester. [c] Products were isolated by preparative vpc on a 20 ft × 0.25 in. column containing 25% SE-30 on Chromosorb W. [d] Due to decomposition good elemental analysis could not be obtained; however, the structure was strongly supported by ir spectra. [e] Yield estimated by vpc analysis of reaction mixture. [f] Lit. mp 41.5–42°, bp 127–128° (11 mm): S. M. McElvain and J. P. Schroeder, *J. Amer. Chem. Soc.*, **71**, 47 (1949). [g] Lit. bp 98–102° (13 mm), $n^{25}D$ 1.4215: S. M. McElvain and J. P. Schroeder, *ibid.*, **71**, 40 (1949). [h] Methyl phenylcyanoacetate was isolated.

On slow addition of sodium methoxide to **3** only about 5% of the monomethoxy derivative **15c** was produced

(16) E. A. C. Lucken, *J. Chem. Soc.*, 4240 (1964).
(17) E. T. Strom and J. R. Norton, *J. Amer. Chem. Soc.*, **92**, 2327 (1970).
(18) S. Searles, Jr., R. A. Sanchez, R. L. Soulen, and D. G. Kundiger, *J. Org. Chem.*, **32**, 2655 (1967).
(19) P. Beltrame, P. L. Beltrame, and L. Bellotti, *J. Chem. Soc. B*, 932 (1969).
(20) (a) W. E. Truce and J. A. Simms, *J. Amer. Chem. Soc.*, **78**, 2756 (1965); (b) E. W. Cook, Ph.D. Thesis, University of Colorado, 1965.

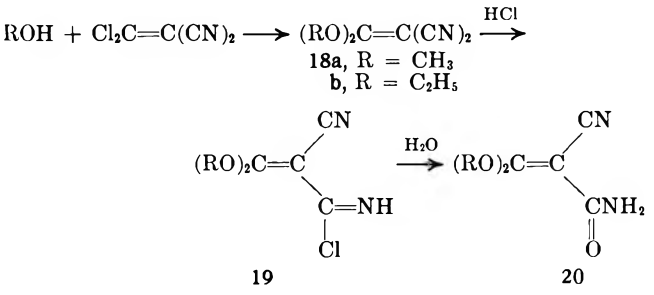
before the ketene acetal **16c** appeared. Further addition of methoxide gave more **16c** but did not increase **15c** concentration to a level where it could be isolated.

Using similar reaction conditions, sodium methoxide and **5** gave a 67% yield of methyl phenylcyanoacetate and two minor components in about 20 and 10% yield.

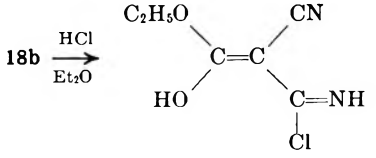
An infrared spectrum of the 20% components gave a strong absorption at 1600 and 2210 cm^{-1} indicative of the ketene acetal **16d**. A second scan of the same sample after 1 day gave a spectrum identical to the ester. The other minor component decomposed within a few minutes to the ester; hence, we suspect that it was the more reactive monosubstituted product **15d**. Since precautions had been taken to ensure anhydrous conditions in this reaction, the increased instability of the ketene acetal **16d** must have been due to steric strain caused by the bulky α phenyl group.

No reaction occurred between acrylonitriles **1**, **2**, **3**, **5**, and methanol in the absence of base. The most reactive member of this group (**3**) and refluxing methanol showed no sign of reaction by vpc after 2 weeks.

It was expected that **4** would be the most reactive acrylonitrile of those studied since the vinylic chlorine atoms were activated by two cyano groups. We were surprised, however, to observe that **4** reacted cleanly and exothermically with anhydrous methanol without added base. The initial product of this reaction was undoubtedly 3,3-dimethoxy-2-cyanoacrylonitrile (**18a**) which subsequently reacted with 1 mol of hydrogen chloride yielding the acrylimidyl chloride **19a**.



Similar findings have been reported by Middleton and Engelhardt[21] who observed that ether solutions of dicyanoketene acetals **18** reacted with excess hydrogen chloride to give products in which a cyano group was converted to CCl=NH and one ether bond broken.



We have been unable to detect any alkyl chloride from the reaction of **4** with methyl or ethyl alcohol. Alcoholic ferric chloride tests for enols have also been negative indicating the absence of ether cleavage in these solvents. Hydrolysis of acrylimidyl chlorides (**19**) to the corresponding acrylamides (**20**) occurred readily in aqueous ethanol or dilute sodium carbonate.

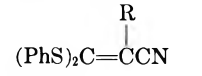
Attempts to react **4** with sodium methoxide gave dark red resinous products confirming the unexpected base sensitive character of dicyanoketene acetals reported previously.[21]

(21) W. J. Middelton and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **80**, 2788 (1958).

Reactions with Sodium Thiophenoxide.—Base-catalyzed reactions of thiophenol with nitriles **1**, **3**, **4**, and **5** proceeded in a straightforward manner to give good yields of 3,3-di(thiophenoxy)acrylonitriles (Table III).

Table III[a]

3,3-Di(thiophenoxy)-2-Substituted Acrylonitriles

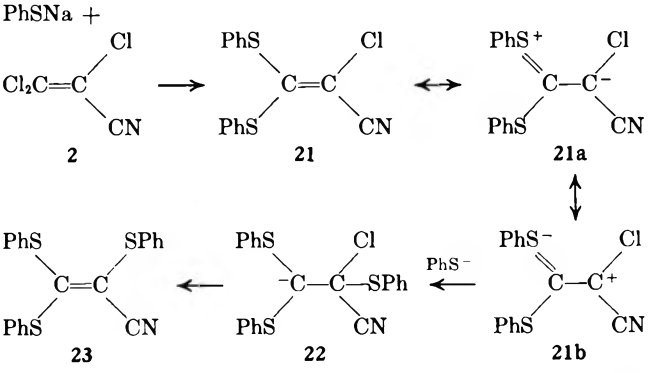


R	Registry no.	Yield, %	Bp (mm) or mp, °C
H	31413-70-4	53	210 (0.025)[b]
Cl	31413-71-5	63	110 (0.08)[c]
CH_3	31413-72-6	40	53.0–54.0
CN	31413-73-7	44	111.5–112.5
SPh	31413-74-8	8[d]	55–58
Ph	31413-75-9	60	104.0–105.0

[a] Satisfactory analytical values (±0.4% for C, H, N, and S) were reported for all compounds except R = Ph (Calcd: C, 73.01. Found: C, 72.39): Ed. [b] $n^{20}D$ 1.665. [c] $n^{20}D$ 1.6706. *Anal.* Calcd: Cl, 11.67. Found: Cl, 11.58. [d] Isolated from preparation of 2-chloro-3,3-di(thiophenoxy)acrylonitrile.

Nitrile **2** reacted with sodium thiophenoxide to give the disubstituted product **21** plus a small amount of a trisubstituted product **23** in which all three chlorine atoms had been replaced. Fortunately, the phenyl ketene thioacetals were quite stable and, if necessary, could be recrystallized from hot aqueous ethanol.

The ability of two β PhS groups to lower the C=C and C≡N stretching frequency in the acrylonitrile system has been discussed above. It becomes more reasonable to ascribe this effect to election withdrawal by the PhS group in view of the unexpected displacement of the α-chlorine atom in **21**.



Three factors may be used in explaining the ability of the thiophenoxide anion to displace the normally inert α-chlorine atom: (a) the high nucleophilic character of the anion, (b) the increased positive charge on the α carbon of **21b**, and (c) the stabilization of the anion in **22** by the PhS group. The last two factors are possible only when the PhS group acts in an electron-withdrawing capacity and effectively competes with the nitrile group for the olefinic π electrons. Similar trisubstituted products of **2** have not been observed with oxygen nucleophiles such as alkoxides or phenoxide nor amines such as aniline or piperidine.[1b,22]

Experimental Section

All melting points were determined on a Fisher-Johns melting points apparatus and are uncorrected. A Varian A-60A spec-

(22) Unpublished reports, this laboratory.

trometer was used to obtain the nmr spectra and a Beckman IR-8 for the infrared spectra. Ultraviolet spectral analysis and elemental analysis were performed by Huffman Laboratories, Wheatridge, Colo., and by Galbraith Laboratories, Knoxville, Tenn.

3,3-Dichloroacrolein (7).—Carbon tetrachloride (2376 g, 15.44 mol) and isobutyl vinyl ether (227.6 g, 2.27 mol) were refluxed for 48 hr during which time 2.0 g of azobisisobutyronitrile was added in small portions. The excess carbon tetrachloride was removed by distillation and the residue heated to 170–180° where copious evolution of HCl occurred. Heating slowly to 220° under slight vacuum caused the dark residue to decompose and a crude mixture of isobutyl chloride and **7** distilled from 107–115°. Redistillation gave 70% yield of **7**, bp 54° (56 mm), n^{24}D 1.5062 [lit.[23] bp 124–125° (atm), $n^{17.5}$D 1.5090].

3,3-Dichloroacrylonitrile (1).—A solution of sodium acetate (123 g, 1.50 mol) in 500 ml of water was added dropwise over a period of 3 hr to an ice-cooled solution of 146.6 g (1.17 mol) of 3,3-dichloroacrolein and 104.3 g (1.50 mol) of hydroxylamine hydrochloride in 600 ml of methanol. The solution was stirred for an additional 2 hr and then concentrated under vacuum at room temperature to *ca.* 700 ml. The liquid oxime layer was removed and the aqueous layer extracted with three 100-ml portions of methylene chloride. The oil and extracts were combined, partially dried with $MgSO_4$, then added to 238 g (2.34 mol) of acetic anhydride, and cooled to 10° overnight. Slow distillation at atmospheric pressure brought about a smooth dehydration of the oxime yielding a mixture of mainly acetic acid and **1**. The fractions containing **1** (104–140°) were combined and slowly added to an ice-cooled mixture of 360 g of $NaHCO_3$ and 700 ml of water. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The extracts and organic layer were combined, dried ($MgSO_4$), and distilled to give 114 g (74%) of **1**: bp 140–141° (745 mm); n^{25}D 1.4922; d^{25}_{25} 1.349 [lit.[c] bp 139–142° (atm)]. *Note:* It is possible to isolate the oxime of **7** as an unstable white solid (mp 38–39°) instead of an oil. Both the solid and the oil contain water of hydration and decompose readily at room temperature. Attempts to dry the solid oxime led to rapid and highly exothermic decomposition.

2,3,3-Trichloroacrylonitrile (2).—2,3,3-Trichloroacrylonitrile was prepared according to the procedure of Boeseker and Du Jardin[6] in an overall yield of 59% from 1,1,2,3,3,3-hexachloropropene. Physical properties for the pure compound (>99% by vpc) were bp 92° (127 mm), d^{25}_{25} 1.5058, n^{25}D 1.5129 (lit.[6] $n^{20.5}$D 1.5100, mp 20°).

3,3-Dichloro-2-methylallyl Alcohol (9).—A mixture of 319 g (2.00 mol) of 1,1,3-trichloro-2-methyl-1-propene and 3,3,3-trichloro-2-methyl-1-propene[24] (80/20 wt % by vpc) and 217 g (2.05 mol) of sodium carbonate in 1500 ml of water was rapidly stirred at reflux temperature for 48 hr. The organic layer was separated and the aqueous layer neutralized with concentrated hydrochloric acid and then extracted with chloroform. The organic layer and chloroform were combined, dried ($MgSO_4$), and then distilled yielding 220.6 g (78% yield) of **9**: bp 93–94° (20–21 mm); $n^{25.2}$D 1.4990; ir (neat) prominent bands were 3310, 1624, 1010, and 80 cm^{-1} [lit.[8] bp 91–92° (16 mm), n^{20}D 1.4998].

3,3-Dichloro-2-methylacrolein (11).—Under a slow N_2 purge, 92.0 g of 3,3-dichloro-2-methylallyl alcohol (0.66 mol) was added dropwise into 650 ml of gently boiling dilute nitric acid (16% HNO_3) containing 0.5 g of V_2O_5. The crude product (73.9 g, 81% yield) was collected in a Barrett trap as it distilled from the reaction mixture. After drying ($MgSO_4$) the light yellow liquid was distilled yielding 56 g (63%) of pure **11**: bp 68–69° (51 mm); n^{25}D 1.5006 [lit.[8] bp 65–66° (50 mm), n^{20}D 1.5045]; ir (neat) prominent bands were 1685, 1588, 1240, 1035, 907 and 705 cm^{-1}.

3,3-Dichloro-2-methylacrolein Oxime (12).—To a solution of 68.5 g (0.50 mol) of sodium acetate trihydrate and 35.8 g (0.50 mol) of hydroxylamine hydrochloride in 200 ml of methanol was added 56.6 g (0.41 mol) of **11**. The mixture was stirred overnight and then poured into 500 ml of ice water and the white precipitate was filtered and dried over phosphorus pentoxide. The crude oxime **12**, 55.8 g (91%), mp 81–82° (lit.[8] mp 84.5–85.5°), was used without further purification.

In a similar experiment the reaction mixture was heated to reflux for 2 hr and then poured into ice water. In addition to a much lower yield of the oxime (21%) there was also obtained a 16% yield of *O*-(3,3-dichloro-2-methyl-1-methoxyallyl)-3,3-dichloro-2-methylacrolein oxime as a stable yellow liquid: bp 108–110° (0.40 mm); n^{28}D 1.5318; ir (neat) prominent bands at 2935, 2840, 1628, 1598, 1570, 1105, 1050, 968, 914, and 900 cm^{-1}; nmr (neat) gave singlets at δ 1.90, 2.00, 3.48, 5.93 and 8.20 in the ratio 3:3:3:1:1.

Anal. Calcd for $C_9H_{11}Cl_4NO_2$: C, 35.21; H, 3.61; Cl, 46.19; N, 4.56. Found: C, 34.96; H, 3.67; Cl, 46.21; N, 4.64.

3,3-Dichloro-2-methylacrylonitrile (3).—A mixture of 26.5 g (0.26 mol) of acetic anhydride and 20.0 g (0.13 mol) of dry **12** was heated to gentle reflux for 3 hr and then 24.4 g of acetic acid and some acetic anhydride were removed by slow distillation. The light brown residue was washed with 100 ml of water containing 0.13 mol of sodium carbonate. The organic layer was removed by chloroform extraction, dried over calcium chloride, and then distilled to yield chloroform and 12.6 g (71%) of **3**, bp 65–67° (25 mm), n^{25}D 1.4873.

Anal. Calcd for $C_4H_3Cl_2N$: C, 35.33; H, 2.22; Cl, 52.14; N, 10.30. Found: C, 35.47; H, 2.31; Cl, 52.08; N, 10.23.

1,1-Dichloro-2,2-dicyanoethylene (4).—The procedure of Josey, *et al.*,[10] was used to prepare **4**, mp 61.0–61.5° (lit.[10] mp 61.5–62°).

3,3-Dichloro-2-phenylacrylonitrile (5).—A mixture of 178.0 g (0.680 mol) of triphenylphosphine, 45.0 g (0.343 mol) of benzoyl cyanide,[11] and 400 ml of dry carbon tetrachloride was stirred at room temperature overnight and then heated to gentle reflux for 4 hr. The mixture was cooled, 600 ml of ligroin added, and the precipitate of triphenylphosphine oxide collected. The filtrate was concentrated under reduced pressure and then vacuum distilled yielding 49.1 g (73%) of **5**, bp 101–104° (0.4 mm), $n^{25.0}$D 1.5866.

Anal. Calcd for $C_9H_5Cl_2N$: C, 54.58; H, 2.54; N, 7.07; Cl, 35.80. Found: C, 54.76; H, 2.74; N, 7.28; Cl, 35.84.

Reactions with Sodium Methoxide. General Procedure.—Anhydrous methanol was prepared by refluxing reagent grade methanol with calcium hydride for 24 hr and then collecting a center cut.

A solution of sodium methoxide in methanol was added slowly to an ice-cooled mixture of the acrylonitrile in methanol. Product formation was monitored by repeated vpc analysis of the reaction mixture. After addition of the methoxide the solution was stirred for a period (0.5–3.0 hr), then the methanol was removed by vacuum, and the residue filtered. The product was isolated from the filtrate by distillation through a micro distillation still or by vpc separation on a 20 ft × 0.25 in. column containing 25% SE-30 on Chromosorb W, 60–80 mesh. These reactions were usually carried out on a 0.05-mol scale. All products, especially the monosubstituted derivatives, were quite unstable and began decomposition within a few days at room temperature. The results are summarized in Table II.

2-Cyano-3,3-dimethoxyacrylamide (20a).—Anhydrous methanol (50 ml) was added to 3.00 g (0.0204 mol) of **4** under a N_2 atmosphere. After an initial exothermic reaction the mixture was heated to reflux for 3 days, concentrated under vacuum, and then the residue was poured into 100 ml of 5% sodium carbonate. The resulting light yellow precipitate was recrystallized from aqueous methanol to give 1.30 g (41%) of **20a**: mp 212–213°; ir (KBr pellet) prominent bands at 3300 and 3180 broad, 2210 sh, 1680 m, 1645 s, 1510 s, and 1125 cm^{-1} s.

Anal. Calcd for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.51; H, 5.26; N, 17.84.

2-Cyano-3,3-diethoxyacrylamide (20b).—Anhydrous ethanol (30 ml) and 3.00 g (0.0204 mol) of **4** were heated to reflux for 3 days and then cooled and a light yellow precipitate was collected. The hygroscopic precipitate gave a positive alcoholic $AgNO_3$ test and a negative ferric chloride test for enols and decomposed at 240° in a sealed tube. The precipitate was recrystallized from 95% ethanol yielding 2.47 g (66%) of **20b** as white needles: mp 137.5–138.5°; ir (KBr pellet) prominent bands at 3290 broad, 3140 broad, 2210 sh, 1660 s, 1640 s, 1510 s, 1310 m, 1115 s, and 1080 cm^{-1} m.

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 51.87; H, 6.74; N, 15.18.

Reactions with Sodium Thiophenoxide. General Procedure.—A solution of sodium methoxide (1.9 equiv) and thiophenol (2.1 equiv) in methanol was added dropwise to an ice-cooled solution of the acrylonitrile (1.0 equiv) in methanol. The reaction mixture was stirred at room temperature for 24–48 hr and then filtered and evaporated to dryness. The residue was dis-

(23) M. Levas, *Ann. Chim. (Paris)*, **7**, 697 (1952).

(24) The allylic isomers were prepared by the procedure of D. G. Kundiger, H. Pledger, and L. E. Ott, *J. Amer. Chem. Soc.*, **77**, 6659 (1955).

tilled or recrystallized from benzene–ligroin mixtures. These reactions were carried out using 0.02–0.04 mol of the nitrile. The results are summarized in Table III.

Registry No.—**1**, 7436-85-3; **2**, 16212-28-5; **3**, 31413-58-8; **4**, 10472-00-1; **5**, 31413-60-2; **15a**, 31413-61-3; **15b**, 31413-62-4; **16a**, 15732-02-2; **16b**, 31413-64-6; **16c**, 31413-65-7; **17b**, 31413-66-8; **17c**, 31413-67-9; **20a**, 31413-68-0; **20b**, 31413-69-1; sodium methoxide, 124-41-4; *O*-(3,3-dichloro-2-methyl-1-methoxyallyl)-3,3-dichloro-2-methylacrolein, 31443-67-1.

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Carbodiimide–Sulfoxide Reactions. XI.[1a] Reactions of Carboxylic Acids, Hydroxamic Acids, and Amides

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The mild acid-catalyzed reactions of DMSO and DCC with carboxylic acids, hydroxamic acids, and carboxamides have been examined. Reactions with carboxylic acids, or with the corresponding hydroxamic acids, lead to methylthiomethyl esters and to *N*-acylureas. In the case of hydroxamic acids, minor amounts of products arising from rearrangements of the Lossen type are also found. In the case of *N*-methoxy-*p*-nitrobenzamide, the major product is the *N*-(1,3-dicyclohexyl-1-ureidomethyl) derivative and lesser amounts of methylthiomethyl *N*-methoxy-*p*-nitrobenzimidates are also formed. Primary carboxamides in both the aromatic and aliphatic series react readily to form *N*-acylsulfilimines which can be oxidized to the corresponding *N*-acylsulfoximines. Nitriles are also formed in these reactions. Comparable reactions of amides with DMSO and phosphorus pentoxide or acetic anhydride gave only minor amounts of *N*-acylsulfilimines, the major products being *N,N'*-methylenebiscarboxamides. Photolysis of *N*-acylsulfilimines is shown to proceed primarily *via* formation of an acylnitrene which can either react with the solvent or rearrange to an isocyanate.

Previous papers in this series have shown that dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) react in the presence of a mild acidic catalyst to form the oxysulfonium intermediate **1**. This species can then be attacked by various nucleophiles such as alcohols,[2] phenols,[3] enols,[4] and oximes,[5] leading to dimethylsulfonium intermediates which can undergo oxidation, rearrangement, or a variety of other reactions. In the case of the reactions of alcohols, the mechanism of the oxidation reaction has been quite carefully studied using isotopes.[1,2b] In the present paper these studies have been extended to cover the acid-catalyzed reactions of DMSO and DCC with carboxylic acids, hydroxamic acids, and carboxamides. In view of the mechanistic similarities of these reactions to those using DMSO activated by acetic anhydride[6] or phosphorus pentoxide,[7] several comparable reactions have been studied using these reagent mixtures.

Our initial reactions were done using *p*-nitrobenzoic acid, which reacted exothermically with 3 molar equiv of DDC and 0.5 molar equiv of anhydrous orthophosphoric acid in a mixture of DMSO and benzene. Following destruction of excess DCC with oxalic acid,[8] two crystalline products were readily isolated and shown to be methylthiomethyl *p*-nitrobenzoate (**5a**) and 1-*p*-nitrobenzoyl-1,3-dicyclohexylurea (**7a**) in yields of 40 and 42%. The formation of methylthiomethyl esters has also been demonstrated by Onodera, *et al.*,[9] following reactions of carboxylic acids with DMSO and phosphorus pentoxide at 70° and can, in both cases, be considered as the products of Pummerer-type rearrangements[10] of the acyloxysulfonium ylide (**3**) according to Scheme I.

The ylide **3** is written as arising *via* the tetracovalent sulfur intermediate **2**, but, as has been discussed in our work on the oxidation of alcohols,[1] could also be formed by a concerted process without accumulation of **2**. Dissociation of the ylide into the methylene methylsulfonium ion **4** and recombination with the carboxylate anion to give **5** is typical of the Pummerer reaction[10] and is similar to what has been previously proposed for the reactions of oximes[5] and 2,6-disubstituted phenols.[3b] An alternative route involving initial reaction of the carboxylic acid with DCC to form the corresponding acid anhydride followed by a typical Pummerer reaction with DMSO cannot be excluded. Indeed, *p*-nitrobenzoic anhydride[11] has been found to react very rapidly with DMSO to form **5a**.

In our previous papers we have considered the direct product of the reaction of an oxygen nucleophile with the DMSO–DCC adduct **1** to be an oxysulfonium salt which subsequently readily loses a proton to form the sulfonium ylide (*e.g.*, **3**). Based upon our more recent results[1] on the mechanism of the DMSO–DCC oxidation of alcohols, however, direct formation of the ylide

(1) (a) For part X, see J. G. Moffatt, *J. Org. Chem.*, **36**, 1909 (1971); (b) Syntex Postdoctoral Fellow, 1966–1968.

(2) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965); (b) A. H. Fenselau and J. G. Moffatt, *ibid.*, **88**, 1762 (1966); (c) for a review see J. G. Moffatt in "Techniques and Applications in Organic Synthesis: Oxidation," Vol. 2, R. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N. Y., in press.

(3) (a) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); (b) M. G. Burdon and J. G. Moffatt, *ibid.*, **89**, 4725 (1967).

(4) A. F. Cook and J. G. Moffatt, *ibid.*, **90**, 740 (1968).

(5) A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).

(6) (a) J. D. Albright and L. Goldman, *ibid.*, **30**, 1107 (1965); (b) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967); (c) Y. Hayashi and R. Oda, *J. Org. Chem.*, **32**, 457 (1967); (d) A. Hochrainer and F. Wessely, *Monatsh. Chem.*, **97**, 1 (1966).

(7) K. Onodera, S. Hirano, and N. Kashimura, *Carbohyd. Res.*, **6**, 276 (1968).

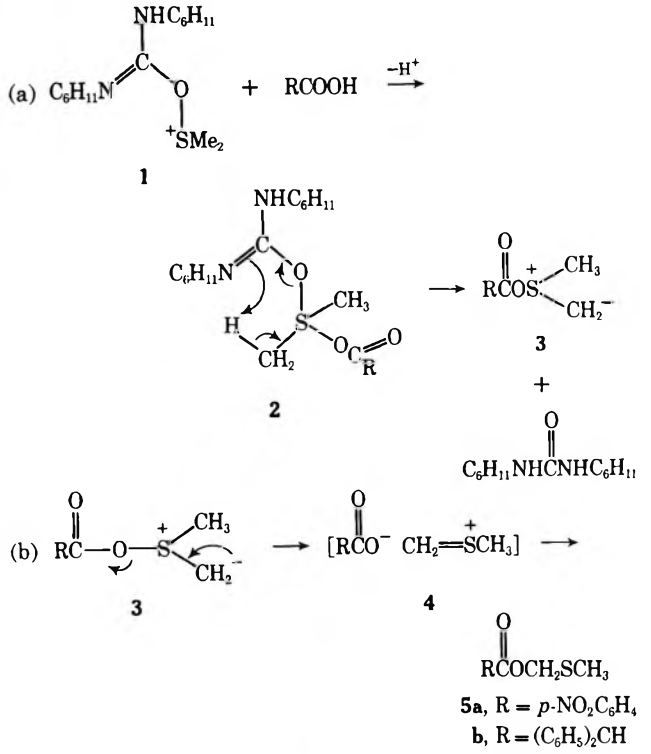
(8) F. Zetzsche and H. Lindler, *Chem., Ber.*, **71B**, 2095 (1938)

(9) K. Onodera, S. Hirano, N. Kashimura, and T. Yajima, *Tetrahedron Lett.*, 4327 (1965).

(10) G. A. Russell and G. J. Mikol in "Mechanism of Molecular Migrations," Vol. 1, B. A. Thyagarajan, Ed., Interscience, New York, N. Y., 1968, p 157.

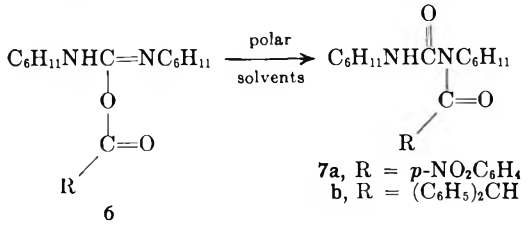
(11) H. Rinderknecht and V. Ma, *Helv. Chim. Acta*, **47**, 163 (1964).

SCHEME I



via a cyclic process (*e.g.*, **2** → **3**) is indicated and probably also obtains in reactions involving other nucleophiles such as phenols, oximes, etc.

Formation of the *N*-acylurea **7a** is probably due to direct reaction of the carboxylic acid with DCC, rearrangement of the initial adduct **6** being well known in polar solvents.[12]

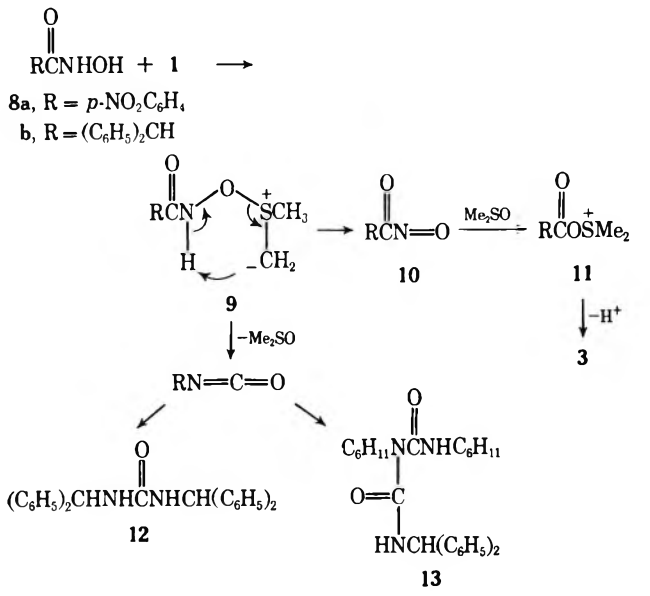


As might be expected, the reaction of *p*-nitrobenzoic acid with DMSO and acetic anhydride at room temperature also gave the methylthiomethyl ester **5a** presumably *via* the ylide **3**. The reaction was, however, slow and after 3 days the isolated yield of **5a** was only 33%. As an example of an aliphatic carboxylic acid, diphenylacetic acid was also allowed to react with DMSO and DCC, giving the methylthiomethyl ester **5b** and the *N*-acylurea **7b** in yields of 69 and 26%, respectively. The formation of these two types of products would thus appear to be quite general from a variety of carboxylic acids.

The hydroxamic acids **8a**[13] and **8b**[14] derived from *p*-nitrobenzoic and diphenylacetic acids were also allowed to react with DMSO and DCC in the presence of anhydrous phosphoric acid. The reaction with **8a** gave the same methylthiomethyl ester **5a** (31%) and acylurea **7a** (42%) as were obtained from the acid, and similarly **8b** gave **5b** and **7b** in yields of 50 and 15%. In addition, the reaction of **8b** gave low yields of two crystalline products identified as 1,3-dibenzhydrylurea (**12**, 10%[15]) and 1,3-dicyclohexyl-1-(benzhydrylaminocarbonyl)urea (**13**, 2%). Both of these minor products would appear to arise *via* a Lossen-type rearrangement[16] of the hydroxamic acid to give benzhydrylisocyanate, which can then react with either benzhydrylamine or dicyclohexylurea. Activation of the hydroxamic acid as a prelude to isocyanate formation could involve either direct reaction with DCC[17] or protonation of the ylide **9**. The related activation of certain oximes as their oxysulfonium derivatives has previously been used to rationalize DMSO–DCC promoted Beckmann rearrangements.[5]

Since the major reaction products starting from either carboxylic acids or the corresponding hydroxamic acids are the same, it is interesting to speculate as to at which point the two reaction pathways become equivalent. A likely probability (Scheme II) is that reaction

SCHEME II



of the hydroxamic acid with the DMSO–DCC adduct **1** leads, as in Scheme I, to an oxysulfonium ylide **9** that collapses intramolecularly to dimethyl sulfide and the nitroso compound **10**. The latter type of compound has been postulated as a reactive intermediate during oxidation of hydroxamic acids with a variety of agents[18] and thermal decomposition of nitrite esters.[19] Reactions of **10** with DMSO would then give the oxysulfonium salt **11** which, by ready loss of a proton, would give the same ylide **3** as arose from the acid itself. By cyclic proton abstractions similar to **9** → **10**, the nitroso compound **10** could be formed regardless of whether the nucleophilic center of **8** was either of the oxygen atoms or the nitrogen of the hydroxamate function.

(12) For review see (a) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953); (b) F. Kurzer and K. Douraghi-Zadek, *ibid.*, **67**, 107 (1967).

(13) B. E. Hackley, R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **77**, 3631 (1955).

(14) L. W. Jones and C. D. Hurd, *ibid.*, **43**, 2432 (1921).

(15) A. Rahman and M. O. Farooq, *Justus Liebigs Ann. Chem.*, **585**, 200 (1953).

(16) H. L. Yale, *Chem. Rev.*, **33**, 209 (1943).

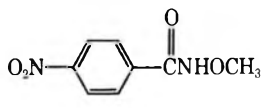
(17) (a) K. Nagarajan, S. Radjappa, and V. S. Iyer, *Tetrahedron*, **23**, 1049 (1967); (b) D. G. Hoare, A. Olson, and D. E. Koshland, *J. Amer. Chem. Soc.*, **90**, 1638 (1968).

(18) (a) B. Szlark and A. F. Al-Sayyab, *J. Chem. Soc.*, 1318 (1964); (b) J. E. Rowe and A. D. Ward, *Aust. J. Chem.*, **21**, 2761 (1968).

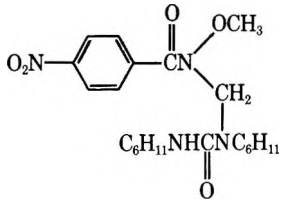
(19) A. L. J. Beckwith and G. W. Evans, *J. Chem. Soc.*, 130 (1962).

In order to avoid the formation of nitroso compounds by the pathway **8** → **10**, *N*-methoxy-*p*-nitrobenzamide (**14**) was prepared and allowed to react in the usual way, giving one major and two minor products in addition to a number of unidentified by-products. The major product, isolated in yields up to 69%, has only been obtained as an extremely viscous, chromatographically homogeneous syrup that decomposes upon attempted short path distillation into **14** and dicyclohexylurea. From its analysis and nmr spectrum this product is clearly a dicyclohexylurea adduct and is assigned the structure *N*-(1,3-dicyclohexyl-1-ureidomethyl)-*N*-methoxy-*p*-nitrobenzamide (**15**). In addition to the expected cyclohexyl, methoxyl, and aromatic protons, the NCH_2N group appears as a two-proton singlet at 5.25 ppm. That this compound has the structure **15** rather than being the isomeric imido ester is confirmed by its ultraviolet spectrum, which is very similar to that of **14** and totally unlike those of **16** and **17**. As expected, treatment of **15** with aqueous acid resulted in its rapid hydrolysis to dicyclohexylurea, **14**, and formaldehyde, the latter being isolated as its dinitrophenylhydrazone.

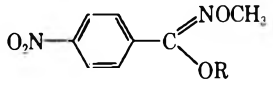
The other major products from reaction of **14** proved to be the syn (5%) and anti (10%) forms of methylthiomethyl *N*-methoxy-*p*-nitrobenzimidate (**16a** and **17a**). That these compounds were indeed imido esters rather than their N-alkylated isomers was shown by the close similarity of their ultraviolet spectra to those of the correspondingly ethyl *N*-methoxy-*p*-nitrobenzimidates (**16b**, **17b**) rather than to **14**. The preparation of **16b** and **17b** was readily achieved by alkylation of **14**



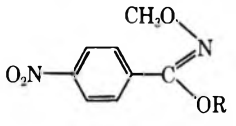
14



15



16a, R = CH_2SCH_3
b, R = Et

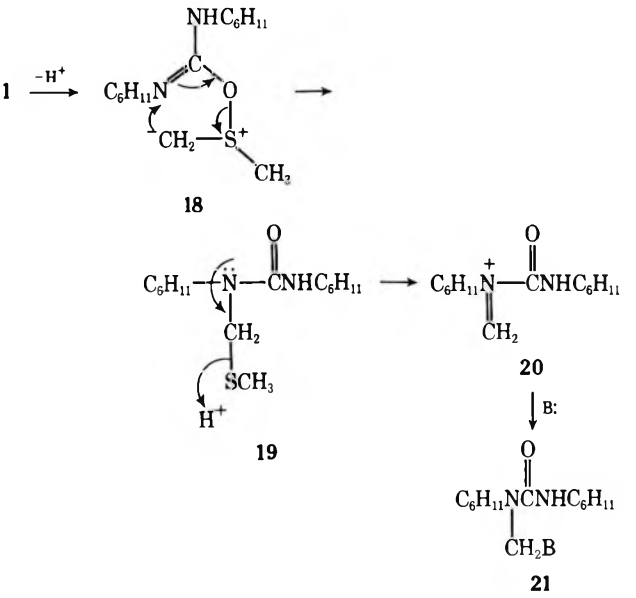


17a, R = CH_2SCH_3
b, R = Et

with triethyloxonium fluoroborate, a reagent well known to effect O-alkylation of amides.[20] The assignment of stereochemistry to **16** and **17** is based upon nmr spectroscopy and an extension of the empirical rules developed for oximes.[21] Thus, in the more polar syn isomers (**16a** and **16b**) the OCH_2S and OCH_2CH_3 protons are deshielded by the methoxyl group and are shifted downfield 0.24 and 0.25 ppm relative to their anti counterparts. It is interesting to note that in simple oximes of ethyl ketones, the deshielding effect of the hydroxyl group is not noticeable in the β-methyl group.[21b]

We have previously observed[3a] the formation of compounds similar to **15** in which a 1,3-dicyclohexyl-1-ureidomethyl group is attached to a nucleophilic center, and many further examples of this type of compound will be found in this paper. These compounds usually appear to arise only during reactions that are rather slow and are, unlike **15**, generally minor products. We tentatively propose the mechanism outlined in Scheme III for the formation of these compounds.

SCHEME III



From previous studies[1] we know that there is not extensive accumulation of **1** in DMSO–DCC reactions in the absence of a nucleophile. In the presence of relatively poor nucleophiles there is ample opportunity for loss of a proton from **1**, forming a stabilized oxysulfonium ylide **18** which can rearrange *via* a cyclic mechanism forming the *N*-(methylthiomethyl)urea **19** and then lose methyl mercaptan giving the iminium ion **20**. The latter species could then react with a nucleophile forming the observed ureidomethyl derivatives **21**. We have not isolated compound **19** from any DMSO–DCC reaction, but comparable, acid-catalyzed decompositions of compounds containing NCH_2SCH_3 functions appear to adequately explain the formation of a variety of products described in this and a forthcoming paper.[22] It is perhaps surprising that **15** proves to be an N-substituted derivative, since it is known that acylation[23] or alkylation with diazomethane[24] or oxonium salts (see above) of *N*-alkoxy arylcarboxamides leads predominantly to O-substituted products.

The formation of the imido esters **16a** and **17a** probably occurs by a dissociation–recombination mechanism *via* the sulfonium ylide **22**. A similar mechanism could also involve an initial oxysulfonium ylide rather than **22**, but in view of our results on the reactions of simple amides, we prefer the nitrogen of **14** as the original nucleophile. An alternative cyclic intramolecular

(20) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

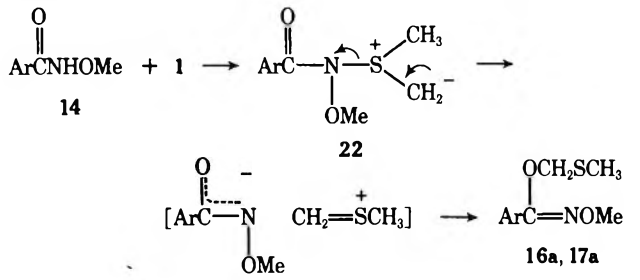
(21) (a) I. Pejković-Tadić, M. Hranisavljević-Jakovljević, S. Nesić, C. Pascual, and W. Simon, *Helv. Chim. Acta*, **48**, 1157 (1965); (b) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3347 (1968).

(22) U. Lerch and J. G. Moffatt, *J. Org. Chem.*, in press.

(23) M. T. W. Hearn and A. D. Ward, *Aust. J. Chem.*, **22**, 161 (1969).

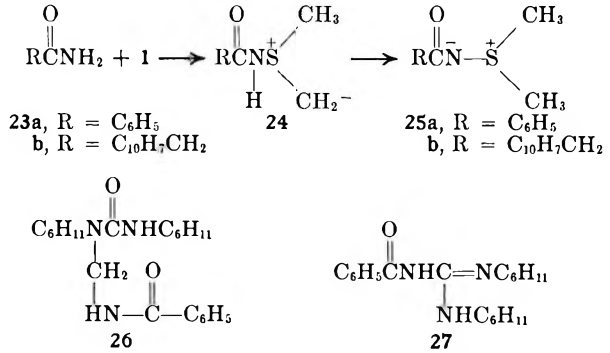
(24) R. Blaser, P. Imfeld, and U. Schindler, *Helv. Chim. Acta*, **52**, 569 (1969).

rearrangement of **22** to **16a** or **17a** is less likely, since it involves nucleophilic attack of the ylide carbanion on oxygen.

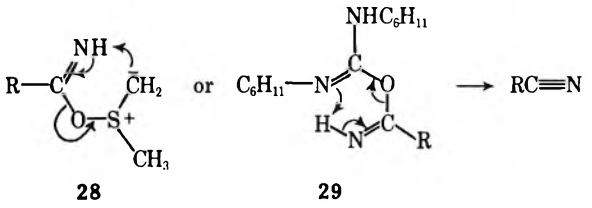


We next turned our attention to the reactions of amides and found that simple primary carboxamides **23** rapidly react with sulfoxides and DCC to form *N*-acyl-*S*,*S*-dialkylsulfilimines (**25**).[25] While *N*-sulfonylsulfilimines have been prepared by many routes,[25] including the reactions of sulfonamides with DMSO and phosphorus pentoxide or acetic anhydride, the latter reactions have been claimed to work only with amides of very strong carboxylic acids (*e.g.*, dichloro- and trichloroacetamide)[26] and *N*-acylsulfilimines have remained relatively poorly studied. The preparation of *N*-benzoyl-*S*,*S*-dimethylsulfilimine (**25a**) has, for example, only very recently been achieved *via* photolysis of 3-phenyl-Δ^2-1,4,2-dioxazolin-5-one in dimethyl sulfide.[27] The reaction of benzamide with DMSO and DCC in the presence of anhydrous orthophosphoric acid, however, rapidly gave **25a** in a yield of 47% together with 12% benzonitrile, and several minor byproducts identified as *N*-(1,3-dicyclohexyl-1-ureidomethyl)benzamide (**26**) and 1-benzoyl-2,3-dicyclohexylguanidine (**27**)[28] by analytical and spectroscopic methods.

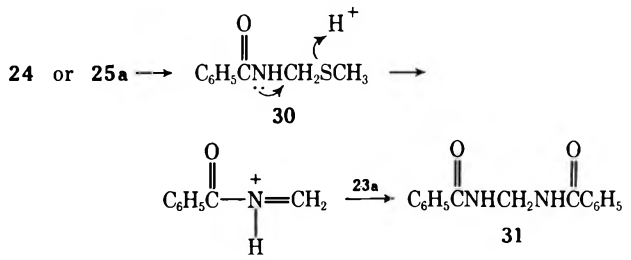
The formation of **25** presumably proceeds *via* initial condensation of the amide with **1** giving the sulfonium ylide **24**, which undergoes a rapid prototropic shift of the labile NH proton to the more stable sulfilimine form.



The formation of benzonitrile in the above reaction may well be the consequence of a competing initial attack of the amide oxygen upon **1** giving the oxysulfonium ylide **28**, which can collapse *via* a cyclic process to the nitrile. An alternative direct dehydration involving only DCC and not DMSO cannot, however, be ruled out, since it was shown that benzonitrile is also formed by reaction of benzamide with DCC and anhydrous phosphoric acid in dimethylformamide, presumably *via* the intermediate **29**. The guanidine **27** can arise *via* the alternative acid-catalyzed addition of the benzamide nitrogen to DCC, while **26** is typical of compounds originating from **20**.



In contrast to the results above, the reactions of benzamide with DMSO and phosphorus pentoxide or acetic anhydride took largely different courses. Thus, the reaction of **23a** with DMSO and phosphorus pentoxide at room temperature gave **25a** in only 13% yield, while the major product (61%) was *N*,*N*′-methylenebisbenzamide (**31**). The latter compound is a well-known product from strong heating of either benzamide[29] or benzonitrile[30] with sulfuric acid in DMSO and has been attributed to condensations with formaldehyde arising from decomposition of DMSO. Similarly, the reaction of benzamide with DMSO and acetic anhydride at 115° gave **31** in 35% yield, although in this case little reaction occurred at room temperature or at 70°. It is not clear whether the formation of **31** in the reactions occurs *via* the ylides **24** or **25a** or directly from the amide **23a** with formaldehyde. Preliminary dehydration of **23a** to the nitrile appears not to be involved, since benzonitrile does not react with DMSO and phosphorus pentoxide under the usual reaction conditions. Treatment of **23a** with paraformaldehyde and anhydrous phosphoric acid in DMSO does slowly give **31**, and this reaction is more rapid using sulfuric acid. On the other hand, the ylide **25a** is converted, in 64% yield, into **31** by heating with 0.1 molar equiv of anhydrous phosphoric acid in dimethylformamide. The conversion of **25a** to **31** can also be achieved, albeit in only 13% yield, by heating with acetic anhydride, the major product in this case being *N*-acetylbenzamide.[31] If indeed the ylides **24** or **25a** are the progenitors of **31**, then a mechanism involving initial rearrangement, probably *via* a dissociation–recombination mechanism, to the amide **30** might be considered.



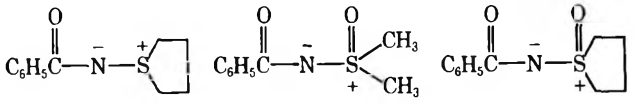
A similar proposal has been made by Sekera and Rumpf[32] to explain the formation of *N*,*N*′-methylenebissulfonamides from sulfonamides and phosphorus pentoxide in DMSO but has been criticized by Martin, *et al.*,[30] for reactions using phenyl cyanate as the activating agent. In the present case, the intermediacy of

(25) For a review on sulfilimines see F. Challenger in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 339.
(26) D. S. Tarbell and C. Weaver, *J. Amer. Chem. Soc.*, **63**, 3272 (1954).
(27) J. Sauer and K. K. Mayer, *Tetrahedron Lett.*, 319 (1968).
(28) F. L. Scott, *J. Org. Chem.*, **22**, 1568 (1957).
(29) V. J. Traynelis and W. L. Hergenrother, *ibid.*, **29**, 221 (1964).
(30) D. Martin, H. J. Niclas, and A. Weise, *Chem. Ber.*, **102**, 23 (1969).
(31) C. D. Hurd and A. G. Prapas, *J. Org. Chem.*, **24**, 388 (1959).
(32) A. Sekera and P. Rumpf, *C. R. Acad. Sci.*, **260**, 2252 (1965).

25a seems questionable, since treatment of this ylide with DMSO and phosphorus pentoxide at room temperature gives only low yields of 31. Once again, we have no direct evidence for the formation of an intermediate such as 30.

The formation of *N*-acylsulfilimines seems to be a fairly general reaction, since the reaction of β-naphthylacetamide (23b) with DMSO–DCC gave *S,S*-dimethyl-*N*-(β-naphthylacetyl)sulfilimine (25b) in 28% yield together with 31% of β-naphthylacetonitrile.[33] The reaction of benzamide with DCC and anhydrous phosphoric acid in tetramethylene sulfoxide also occurred readily and gave crystalline *N*-benzoyl-*S,S*-tetramethylenesulfilimine (32) in 35% yield together with smaller amounts of benzonitrile and 27. This reaction has not been studied using other activating agents.

Oxidation of both 25a and 32 was readily achieved using aqueous potassium permanganate and gave the corresponding sulfoximines 33 and 34 in high yield. *N*-Acylsulfoximines are better known than *N*-acylsulfilimines, since they can be prepared by photolysis of acylazides in sulfoxides[34] or by acylation of the parent *S,S*-dialkylsulfoximine.[34a,35] Attempted oxidation of 25b, however, gave only β-naphthylacetamide in 90% yield.

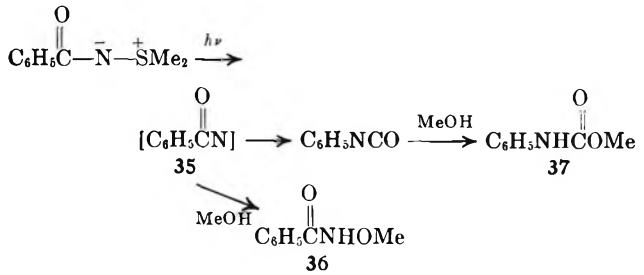


32 33 34

With the ylide 25a readily available, a few other simple reactions on this species were undertaken. As would be expected, treatment of 25a with anhydrous hydrogen chloride in dioxane gave benzamidodimethylsulfonium chloride in high yield. Upon heating at 100° with 2 *N* sodium hydroxide, 25a was hydrolyzed to a mixture of benzamide and benzoic acid, roughly 20 min being required for disappearance of the starting material. It was completely stable in 2 *N* hydrochloric acid at room temperature for 16 hr but was hydrolyzed to benzoic acid upon heating the solution to 100° for 1.5 hr. There was no decomposition at all upon heating 25a in DMSO at 115° for 15 hr.

Irradiation of a solution of 25a in methanol using a low-pressure mercury lamp led quite rapidly to the formation of benzamide (47%), *N*-methoxybenzamide (36, 7%),[36] and methyl carbanilate (37, 33%),[37] all being identical with authentic samples by tlc, infrared and ultraviolet spectroscopy, and gas–liquid chromatography. The formation of the latter two compounds, both of which are also formed during photolysis of benzoylazide in methanol,[34b] suggests photochemical conversion of 25a into the acylnitrene 35,[38] which can then insert into the OH bond of methanol giving 36 or rearrange to phenyl isocyanate, which reacts with methanol giving 37.

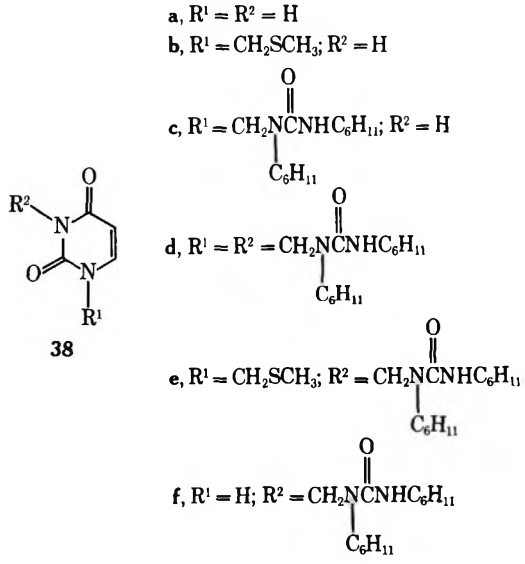
During preparation of authentic 36 through reaction of benzoyl chloride with methoxylamine, the previously undescribed *N*-methoxydibenzamide was isolated in 24% yield.



35 36 37

N-Substituted carboxylic acid amides were found to be much less reactive toward DMSO and DCC. Benzanilide, in fact, was completely inert to even quite prolonged reaction and also failed to react with DMSO and either acetic anhydride or phosphorus pentoxide at room temperature. At 80° with P_2O_5 some reaction did occur, giving a considerable number of unidentified minor products.

In recent years there has been a great deal of work done in this laboratory on the oxidation, using the DMSO–DCC method, of isolated sugar hydroxyl groups in nucleosides to the corresponding aldehydo and keto functions.[39] Usually these oxidations are worked up after 3–12 hr depending upon the choice of acid catalyst, and under these conditions only very minor side reactions are observed. If the reactions are allowed to proceed for several days, however, unidentified by-products do appear, and it was of interest to determine what type of reactions could occur on the heterocyclic bases under these conditions. Our initial study involved the reaction of uracil (38a) with DMSO, DCC, and anhydrous phosphoric acid. A slow reaction took place and after 7 days five new crystalline products in addition to 24% unreacted 38a were isolated by preparative tlc. These were all readily shown to be derivatives in which either or both of N_1 or N_3 of the uracil ring are substituted by methylthiomethyl or 1,3-dicyclohexyl-1-ureidomethyl groups. Based upon elemental analysis and nmr and



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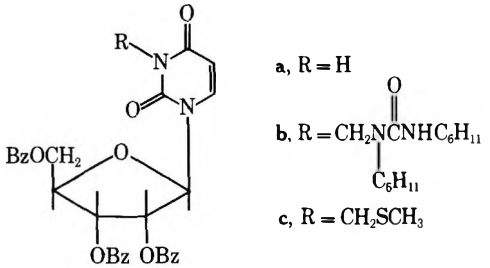
(33) S. C. J. Oliver and J. Wit, *Recl. Trav. Chim. Pays-Bas*, **57**, 90 (1938).
(34) (a) L. Horner and A. Christmann, *Chem. Ber.*, **96**, 388 (1963); (b) L. Horner, G. Bauer, and J. Dourges, *ibid.*, **98**, 2631 (1965).
(35) F. Misani, T. H. Fair, and L. Reiner, *J. Amer. Chem. Soc.*, **73**, 459 (1951).
(36) W. Lossen, *Justus Liebigs Ann. Chem.*, **281**, 186 (1894).
(37) A. W. Hofmann, *ibid.*, **74**, 1 (1850).
(38) For a review of acylnitrenes see W. Lwowski in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, p 185.
(39) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963); (b) A. F. Cook and J. G. Moffatt, *ibid.*, **89**, 2697 (1967); (c) U. Brodbeck and J. G. Moffatt, *J. Org. Chem.*, **35**, 3552 (1970); (d) unpublished experiments of G. H. Jones, G. B. Howarth, N. P. Damodaran, and J. G. Moffatt.

ultraviolet spectra these compounds have been identified as **38b–f**.

The major products (**38b** and **38c**) were shown to be N^1-substituted uracils by their ultraviolet spectra under neutral and alkaline conditions, which closely resemble those of 1-methyluraeil [$\lambda_{max}^{pH\ 7}$ 267 mμ (ε 9700); $\lambda_{max}^{pH\ 12}$ 265 mμ (ε 7000); $\epsilon_{max}^{pH\ 7}/\epsilon_{max}^{pH\ 12} = 1.37$][40] rather than those of 3-methyluracil [$\lambda_{max}^{pH\ 7}$ 259 mμ (ε 7300); $\lambda_{max}^{pH\ 12}$ 283 mμ (ε 10,700); $\epsilon_{max}^{pH\ 7}/\epsilon_{max}^{pH\ 12} = 0.68$].[40] In addition, desulfurization of **38b** gave 1-methyluracil in crystalline form. The 3-substituted uracil derivative **38f** had spectral properties very similar to those of 3-methyluracil and unlike those of the 1-methyl isomer. The orientation of the two substitutents in **38e** could be ascertained by the rather facile decomposition of this compound into **38b**, thus placing the methylthiomethyl group at N^1. A similar instability of **38d** with loss of the ureidomethyl group from N^3 and formation of **38c** was also noted.

The possible reactions occurring with 2′,3′,5′-tri-*O*-benzoyluridine (**39a**)[41] are obviously fewer in number and closer to our direct interest. Once again, a slow reaction occurred using anhydrous phosphoric acid as the proton source with roughly 10–20% conversion after 24 hr and 50% after 5 days. Since an oxidation reaction using this acid is generally complete within 1–2 hr, no appreciable side reactions involving the uracil ring would be expected to occur within this time. Careful preparative tlc separated the reaction product into two bands, the major one of which (40%) was shown to be N^3-(1,3-dicyclohexyl-1-ureidomethyl)-2′,3′,5′-tri-*O*-benzoyluridine (**39b**), which was obtained in an analytically pure form. The ultraviolet spectrum of this compound was consistent with it being an N^3-substituted uracil rather than an O^4-substituted compound. The minor product proved to be N^3-methylthiomethyl-2′,3′,5′-tri-*O*-benzoyluridine (**39c**), the structure of which was immediately obvious from its nmr spectrum. The spectrum of **39c** was somewhat unique in that the NCH_2S protons in the N^3 substituent were magnetically nonequivalent, presumably due to restricted rotation, and appeared as an AB quartet (J_{gem} = 13 Hz) centered at 4.95 ppm. Most other compounds containing the NCH_2SCH_3 grouping that we have encountered have given nmr spectra in which the NCH_2S protons appear as a singlet.



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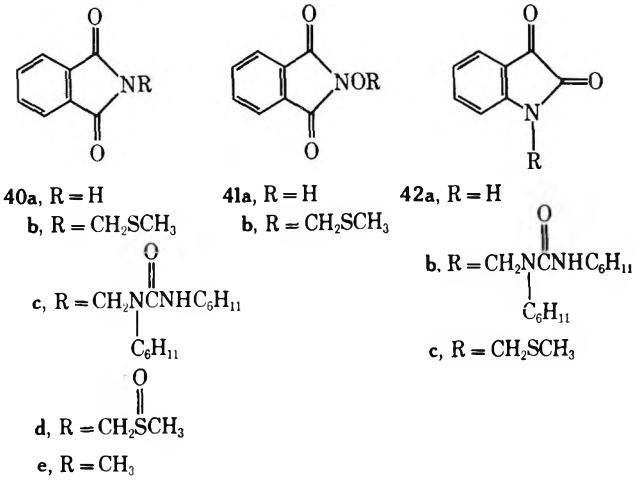
Very similar types of compounds were obtained from the reaction of phthalimide (**40a**) with DMSO and DCC, the major product in this case being *N*-(methylthiomethyl)phthalimide (**40b**, 38%) while the *N*-(ureidomethyl) compound **40c** was formed in only 2% yield. It is not clear why the ureidomethyl derivative should predominate in the reaction of **39a** and be so suppressed with **40a**. Desulfurization of **40b** gave *N*-methylphthalimide (**40e**) identical with an authentic sample.[42] A similar reaction with *N*-hydroxyphthalimide (**41a**) was quite rapid and gave *N*-(methylthiomethoxy)-phthalimide (**41b**) in 58% yield. In this case, there was no sign of a ureidomethyl derivative.

The nmr spectrum of **41b** was somewhat unusual, since the signals for both the SMe (2.38 ppm) and OCH_2S (5.30 ppm) groups are shifted downfield from the normal positions in methylthiomethyl ethers (about 2.1 and 4.7 ppm, respectively).[2a] The SMe signal is, in fact, closer to that expected for a methyl sulfoxide such as **40d**, but this structure is ruled out both by an independent synthesis of **41b** from the sodium salt of **41a** and chloromethyl methyl sulfide and by the mass spectrum of **41b**, which shows a base peak at *m/e* 61 ($CH_2{=}S^+CH_3$) which would not be expected from **40d**.

Recently it was shown that *N*-hydroxysuccinimide[43] and *N*-hydroxyglutarimide[44] react with DCC in tetrahydrofuran or acetonitrile to form di- and trimeric products. No such products were observed in the present reaction in DMSO.

Finally, the lactam function of isatin (**24a**) was found to react slowly with DMSO–DCC in the presence of anhydrous phosphoric acid. In addition to 55% unreacted **42a**, the major product was found to be *N*-(1,3-dicyclohexyl-1-ureidomethyl)isatin (**42b**, 24%), and *N*-(methylthiomethyl)isatin (**42c**) was formed in only very low yield.



From the work reported in this paper it is clear that the acid-catalyzed reactions of carboxylic acids, hydroxamic acids, and amides with DMSO and DCC lead to a variety of product types. In forthcoming papers,[22] this type of reaction will be extended to yet other nucleophilic functional groups.

Experimental Section

General Methods.—Thin layer chromatography (tlc) was done on 0.25-mm layers of Merck silica gel GF and the products were visualized by their ultraviolet absorption or by spraying with a 5% solution of ammonium molybdate in 10% sulfuric acid followed by brief heating at 150°. Preparative tlc was done on 20 ×

(40) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).

(41) J. J. Fox, D, Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Amer. Chem. Soc.*, **81**, 178 (1959).

(42) E. J. Sakellarios, *Helv. Chim. Acta*, **29**, 1675 (1946).

(43) H. Gross and L. Bilk, *Tetrahedron*, **24**, 6935 (1968).

(44) H. Jeschkeit, *Z. Chem.*, **9**, 111 (1969).

100 cm glass plates coated with a 1.3-mm layer of merck silica gel HF. Nuclear magnetic resonance spectra were obtained using Varian A-60 or HA-100 spectrometers and are recorded in parts per million downfield from an internal standard of tetramethylsilane. Mass spectra were obtained using an Atlas CH-4 instrument fitted with a direct inlet system. Elemental analyses were performed by Dr. A. Bernhardt, Mülheim, Germany, and other instrumental analyses were performed by the staff of the Analytical Laboratory of Syntex Research.

Reactions with *p*-Nitrobenzoic Acid. A. With DMSO–DCC.—Dicyclohexylcarbodiimide (6.18 g, 30 mmol) was added to a solution of *p*-nitrobenzoic acid (1.67 g, 10 mmol) and anhydrous orthophosphoric acid (1 ml of a 5 *M* solution in anhydrous DMSO) in a mixture of DMSO (10 ml) and benzene (5 ml). After a few minutes the mixture became hot and crystalline dicyclohexylurea separated. After 30 min the mixture was diluted with ethyl acetate and a solution of oxalic acid (2.52 g, 20 mmol) in ethyl acetate was carefully added (gas evolution). After 30 min the dicyclohexylurea was removed by filtration and the filtrate was washed with aqueous bicarbonate and three times with water. The filtrate was dried ($MgSO_4$) and evaporated, leaving a semicrystalline residue that was combined with some solid material that separated during the aqueous extractions and crystallized from hot ethyl acetate, giving 1.50 g (40%) of fine needles, mp 193–195°. This was essentially pure **7a** contaminated with only a trace of dicyclohexylurea. An analytical sample was prepared from acetone: mp 195–196°; λ_{max}^{MeOH} 273 mμ (ε 9300); nmr (DMSO-d_6) 1.0–2.0 (m, 20, cyclohexyl), 3.1 (m, 1, >CHNHCO), 4.1 [m, 1, >CHN(CO–)$_2$], 7.66 (d, 2, J = 8 Hz, Ar), 7.99 (d, 1, J = 7 Hz, NH), 8.22 ppm (d, 2, J = 8 Hz, Ar).

Anal. Calcd for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.29; N, 11.25. Found: C, 64.33; H, 7.67; N, 11.18.

The filtrate from crystallization of **7a** was purified by preparative tlc using $CHCl_3$–CCl_4 (4:1). Elution of the major band gave 0.96 g (42%) of **5a**: mp 52–53°. [recrystallization from hexane raised the melting point to 53.5–54.5° (lit.[9] mp 54–55°); λ_{max}^{MeOH} 259 mμ (ε 13,400); nmr ($CDCl_3$) 2.33 (s, 3, SCH_3), 5.46 (s, 2, SCH_2O), 8.27 ppm (s, 4, Ar).

Anal. Calcd for $C_9H_9NO_4S$: C, 47.57; H, 3.99; H, 6.16; S, 14.11. Found: C, 47.70; H, 4.13; N, 6.01; S, 13.96.

B. With DMSO–Acetic Anhydride.—A solution of *p*-nitrobenzoic acid (1.67 g, 10 mmol) in a mixture of DMSO (15 ml) and acetic anhydride (10 ml) was kept at 23° for 3 days. It was then diluted with ethyl acetate and extracted with water and with aqueous sodium bicarbonate, dried, and evaporated *in vacuo*, leaving 0.88 g of a solid residue. Crystallization from hexane gave 0.75 g (33%) of **5a** identical with that above.

Reaction with Diphenylacetic Acid.—A mixture of diphenylacetic acid (2.12 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous H_3PO_4 (5 mmol) in DMSO (5 ml) and benzene (5 ml) was kept overnight at room temperature. The mixture was diluted with ethyl acetate, filtered, and extracted four times with water. Evaporation of the dried ($MgSO_4$) organic phase left an oil (3.5 g) that was purified by preparative tlc on three plates using benzene–acetone (4:1), giving two main bands. Elution of the slower band gave 1.08 g (26%) of the crystalline *N*-acylurea **7b**, which was recrystallized from ether: mp 161–162°; λ_{max}^{MeOH} 253 mμ (ε 500), 260 (510), and 266 (380); ν_{max} (KBr) 3335, 1665, 1705 cm^{-1}; nmr 0.90–2.0 (m, 20, CH_2), 3.4–4.3 (m, 2, CHN), 5.29 (s, 1, Ar_2CHCO), 6.2 (m, 1, NH), 7.30 ppm (s, 10, Ar); mass spectrum (70 eV) m/e 418 (M^+), 293 ($M^+ - C_6H_{11}NCO$), 194 ($Ar_2C{=}C{=}O$).

Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.47; H, 8.19; N, 6.69. Found: C, 77.32; H, 7.88; N, 6.78.

Elution of the faster band gave 1.87 g (69%) of a homogeneous oil that was distilled in a Kugelrohr apparatus[45] [bath 150° (0.01 mm)], giving 1.6 g of **5b**: mp 31–31.5°; λ_{max}^{MeOH} 252 mμ (ε 500), 258 (600) and 265 (490); nmr ($CDCl_3$) 2.05 (s, 3, SCH_3), 5.06 (s, 1, Ar_2CHCO), 5.17 (s, 2, OCH_2S), 7.30 ppm (s, 10, Ar).

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.55; H, 5.92; N, 11.75; S, 11.77. Found: C, 70.41; H, 5.86; N, 11.66; S, 11.71.

Reaction of *p*-Nitrobenzohydroxamic Acid (8a).—Anhydrous orthophosphoric acid (5 mmol) was added to a soluion of *p*-nitrobenzohydroxamic acid (1.82 g, 10 mmol)[13] and DCC (6.18 g, 30 mmol) in a mixture of DMSO (10 ml) and benzene (5 ml). An exothermic reaction occurred after a few minutes and after 1 hr the mixture was worked up as above giving a mixture almost identical with that from *p*-nitrobenzoic acid. From this, crystalline **5a** and **7a** were isolated in yields of 31 and 42% as above.

Reaction of Diphenylacetohydroxamic Acid (8b).—A solution of **8b** (2.27 g, 10 mmol),[14] DCC (6.18 g, 30 mmol), and anhydrous orthophosphoric acid (5 mmol) in DMSO (10 ml) and benzene (5 ml) was kept overnight. After the usual work-up with ethyl acetate, the mixture was purified by preparative tlc using benzene–ethyl acetate (19:1) giving three major bands. Elution of the fastest band gave 1.36 g (50%) of almost pure **5b** (ir and tlc) containing only a trace of another compound. The latter (75 mg, 2%) was isolated by crystallization from benzene–hexane, mp 153–155°, and identified as **13**: λ_{max}^{MeOH} 253 mμ (ε 450), 258 (490), 265 (360); ν_{max} (KBr) 1635, 1695 cm^{-1}; nmr ($CDCl_3$) 1.0–2.0 (m, 22, C_6H_{11}), 3.06 (d, 1, Ar_2CHNH giving singlet with D_2O–CD_3COOD), 3.0 and 3.7 (m, 1, NH), 4.24 ppm (br s, 10, Ar); mass spectrum (70 eV) m/e 433 (M^+), 308 ($M^+ - C_6H_{11}NCO$), 224 ($C_6H_{11}NHCONHC_6H_{11}$), 209 (Ar_2CHNCO).

Anal. Calcd for $C_{27}H_{35}N_3O_2$: C, 74.79; H, 8.14; N, 9.69. Found: C, 75.04; H, 7.88; N, 9.79.

Elution of the middle band gave 630 mg (15%) of crystalline **7b**, mp 161–162°, while the slowest band gave, after recrystallization from methanol, 191 mg (10%) of **12**: mp 273° (lit.[15] mp 272–273°); λ_{max}^{MeOH} 249 mμ (ε 1600), 255 (1800), 260 (1700); ν_{max} (KBr) 3325, 1640, 1580 cm^{-1}; nmr (DMSO-d_6) 5.86 (d, 2, J = 8 Hz, Ar_2CHNH becoming singlet with CD_3COOD–D_2O), 6.90 (d, 2, J = 8 Hz, Ar_2CHNH), 7.25 ppm (s, 20, Ar).

Anal. Calcd for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14. Found: C, 82.53; H, 6.50; N, 7.14.

***N*-Methoxy-*p*-nitrobenzamide (14).**—A solution of *p*-nitrobenzoyl chloride (3.7 g, 20 mmol) in chloroform (20 ml) was added slowly to a cooled suspension of methoxylamine hydrochloride (1.67 g, 20 mmol) in chloroform (30 ml) and pyridine (5 ml). After 16 hr the solvent was evaporated and the residue was triturated with water. The resulting crystalline product was recrystallized from water and then from ethyl acetate, giving 3.05 g (78%) of **14**: mp 181–183° (lit.[46] mp 180°); λ_{max}^{MeOH} 263 (ε 9700); $\lambda_{max}^{1N\ NaOH}$ 241 mμ (ε 8600), 256 (8500), 352 (5000); nmr (DMSO-d_6) 3.83 (s, 3, OMe), 8.05 and 8.39 ppm (d, 2, J = 8 Hz, Ar).

Reaction of *N*-Methoxy-*p*-nitrobenzamide (14).—Anhydrous orthophosphoric acid (5 mmol) was added to a solution of **14** (1.96 g, 10 mmol) and DCC (6.18 g, 30 mmol) in a mixture of DMSO (10 ml) and benzene (5 ml). After 18 hr the mixture was worked up as usual using ethyl acetate and the organic phase was purified by preparative tlc on three plates using benzene–ethyl acetate (9:1), giving two major ultraviolet absorbing bands and several yellow bands. Elution of the fastest band (567 mg) followed by rechromatography using two passes with benzene–hexane (3:2) gave two bands. Elution of the faster band followed by Kugelrohr distillation[45] gave 256 mg (10%) of the anti imido ester **17a**: mp 33–36°; λ_{max}^{MeOH} 221 mμ (ε 8600), 254 (8600), 299 (6300); ν_{max} (KBr) 1600, 1525, 1350 cm^{-1}; nmr ($CDCl_3$) 2.33 (s, 3, SCH_3), 3.86 (s, 3, OMe), 5.30 (s, 2, OCH_2S), 8.04 and 8.31 ppm (d, 2, J = 8 Hz, Ar).

Anal. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.88; H, 4.72; N, 10.93; S, 12.49. Found: C, 46.96; H, 4.79; N, 10.87; S, 12.44.

The slower band gave 120 mg (5%) of the syn isomer **16a**: nmr ($CDCl_3$) 2.26 (s, 3, SMe), 3.99 (s, 3, OMe), 5.54 (s, 2, OCH_2S), 7.99 and 8.20 ppm (d, 2, J = 9 Hz, Ar). Attempted short-path distillation (60° at 10^{-3} mm) was accompanied by partial decomposition into **14**.

Elution of the major, slow-moving product gave 1.94 g of a yellow oil that was rechromatographed on three preparative plates using two developments with CCl_4–acetone (4:1) giving 1.61 g (38%) of **15** as a very viscous, pale yellow syrup: λ_{max}^{MeOH} 263 mμ (ε 10,300); ν_{max} 1660, 1525, 1350 cm^{-1}; nmr ($CDCl_3$) 1.0–2.1 (m, 20, cyclohexyl), 3.50 (s, 3, OCH_3), 3.9 (m, 2, >CHN), 5.25 (s, 2, NCH_2N), 5.83 (d, 1, J = 7 Hz, NH), 7.90 and 8.31 ppm (d, 2, J = 8 Hz, Ar).

Anal. Calcd for $C_{22}H_{32}N_4O_5$: C, 61.09; H, 7.46; N, 12.96. Found: C, 61.40; H, 7.73; N, 12.49.

In another experiment this compound was isolated in 69% yield. Treatment with 1 *N* hydrochloric acid at 100° for 5 min gave dicyclohexylurea, **14**, and formaldehyde, the latter being isolated as its 2,4-dinitrophenylhydrazone.

Ethyl *N*-Methoxy-*p*-nitrobenzimidate (16b, 17b).—*N*-Methoxy-*p*-nitrobenzamide (0.98 g, 5 mmol) and triethyloxonium fluoroborate (1.1 g, 5.8 mmol)[20] were stirred overnight in carefully dried methylene chloride (2 ml) and nitromethane (2 ml). After

(45) R. Graeve and G. H. Wahl, *J. Chem. Educ.*, **41**, 279 (1964).

(46) Applied Science Laboratories, State College, Pa.

evaporation of most of the solvent, the mixture was dissolved in ether and extracted with 1 *N* sodium hydroxide to remove some residual **14**. Evaporation of the organic phase left 785 mg of a semicrystalline residue containing roughly equal amounts of **16b** and **17b**. Crystallization from hexane gave the pure, more polar syn isomer **16b**: mp 71–73°; λ_{max}^{MeOH} 223 mμ (ε 11,500), 310 (9800); ν_{max} (CCl_4) 1595, 1525, 1355, 1315 cm^{-1}; nmr ($CDCl_3$) 1.38 (t, 3, J = 7 Hz, CH_2CH_3), 3.95 (s, 3, OCH_3), 4.46 (q, 2, J = 7 Hz, OCH_2CH_3), 7.93 and 8.23 ppm (d, 2, J = 9 Hz, Ar).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.40; N, 12.50. Found: C, 53.44; H, 5.30; N, 12.60.

Kugelrohr distillation[45] of the mother liquors (100° at 10^{-2} mm) gave a partially crystalline mixture of **16b** and **17b**, mp 20–60°. Nmr ($CDCl_3$) included the following resonances for the anti isomer: 1.36 (t, 3, J = 7 Hz, CH_2CH_3), 3.78 (s, 3, OCH_3), 4.21 (q, 2, J = Hz, OCH_2CH_3), 7.91 and 8.21 (d, 2, J = 9 Hz, Ar).

Reactions with Benzamide (23a). A. With DMSO–DCC.—Anhydrous phosphoric acid (10 mmol) was added to a solution of benzamide (2.42 g, 20 mmol) and DCC (11.6 g, 56 mmol) in DMSO (5 ml) and benzene (5 ml). The starting material was largely gone after 2 hr and after standing overnight the mixture was worked up with ethyl acetate and oxalic acid. Some products remained in the aqueous extracts and were largely recovered by neutralization to pH 9 followed by repeated extraction with chloroform. The combined organic phases were purified by preparative tlc on four plates using CCl_4–acetone (2:3), giving three main bands. Elution of the slowest band and crystallization from ether gave 1.71 g (47%) of *N*-benzoyl-*S*,*S*-dimethylsulfilimine (**25a**): mp 108–109.5°; λ_{max}^{MeOH} 250 mμ (ε 10,600), 228 (10,300); ν_{max} (KBr) 1595, 1540, 1330 cm^{-1}; nmr ($CDCl_3$) 2.63 (s, 6, SMe_2), 7.35 (m, 3, Ar C_3, C_4, and C_5 H), 7.88 ppm (m, 2, Ar C_2 H and C_6 H); mass spectrum m/e 181 (M^+), 166 (M − CH_3), 149, 134 [Ar(C=O)NMe^+], 105 ($ArCO^+$).

Anal. Calcd for $C_9H_{11}NO_2$: C, 59.63; H, 6.12; N, 7.73; S, 17.69. Found: C, 59.59; H, 6.21; N, 7.81; S, 17.75.

Elution of the middle band gave 168 mg (7%) of unreacted **23a** while rechromatography of the fast band using two developments with CCl_4–acetone (94:6) gave three bands. The fastest of these contained 245 mg (12%) of benzonitrile that was identified by vpc and infrared analysis. The middle band gave 83 mg of an oil that was crystallized from hexane, giving 55 mg (1%) of 1-benzoyl-2,3-dicyclohexylguanidine (**27**): mp 155–156° (lit.[28] mp 155–156°); λ_{max}^{MeOH} 267 mμ (ε 17,500), 238 (sh, 11,000); ν_{max} (KBr) 3300, 1575 cm^{-1}; nmr ($CDCl_3$) 1.0–2.0 (m, 20, cyclohexyl), 3.75 (m, 2, >CHNH–), 7.4 (m, 3, Ar), 8.25 (m, 2, Ar); mass spectrum m/e 327 (M^+), 245 (M − C_6H_{10}).

Anal. Calcd for $C_{20}H_{29}N_3O$: C, 73.36; H, 8.93. Found: C, 73.70; H, 8.78.

Elution of the slowest band gave 274 mg (4%) of *N*-(1,3-dicyclohexyl-1-ureidomethyl)benzamide (**26**): mp 146–148° from ether; λ_{max}^{MeOH} 227 mμ (ε 12,200); ν_{max} (KBr) 3260, 1625, 1540 cm^{-1}; nmr ($CDCl_3$) 1–2 (m, 20, cyclohexyl), 3.8 (m, 2, CHNH–), 4.85 (d, 2, $J_{H,NH}$ = 6 Hz, $-HNCH_2-$), 6.54 (d, 1, J = 6 Hz, $-NHCH_2-$), 7.5 (m, 3, Ar), 7.8 ppm (m, 2, Ar); mass spectrum (15 eV) m/e 357 (M^+), 224 [$C_6H_{11}NH(C=O)NHC_6H_{11}$], 143 ($m/e$ 224 − C_6H_{10}), 121 ($ArCONH_2^+$).

Anal. Calcd for $C_{21}H_{31}N_3O_2$: C, 70.55; H, 8.74; N, 11.75. Found: C, 70.61; H, 8.84; N, 11.93.

Addition of a slight excess of hydrogen chloride in dioxane to a solution of **25a** in acetone led to crystallization of benzamidodimethylsulfonium chloride, which melted with decomposition and gas evolution at 115–130°: λ_{max}^{MeOH} 230 mμ (ε 11,400), 235 (10,600), 244 (11,500); nmr (D_2O) 3.54 (s, 6, SMe_2), 7.84 ppm (m, 5, Ar).

Anal. Calcd for $C_9H_{12}NOSCl$: C, 49.65; H, 5.56; N, 6.43; Cl, 16.29. Found: C, 49.90; H, 5.74; N, 6.63; Cl, 16.29.

B. With Tetramethylene Sulfoxide and DCC.—Benzamide (2.42 g, 20 mmol), DCC (5.8 g, 56 mmol), and anhydrous phosphoric acid (10 mmol) were allowed to react overnight in tetramethylene sulfoxide (4 ml) and benzene (20 ml). The mixture was diluted with acetone (30 ml) and water (2 ml) and after 5 hr was filtered. The filtrate was neutralized with triethylamine, evaporated *in vacuo*, and chromatographed on six preparative plates using CCl_4–acetone (2:3), giving a major, slow-moving band and four faster bands. Elution of the slow band, followed by crystallization from ether, gave 1.45 g (35%) of *N*-benzoyl-*S*,*S*-tetramethylenesulfilimine (**32**): mp 116–117.5°; λ_{max}^{MeOH} 253 mμ (ε 10,800), 227 (10,400); ν_{max} (KBr) 1590, 1535 cm^{-1}; nmr ($CDCl_3$) 2.1 (m, 4, $-CH_2-$), 3.19 (t, 4, $-SCH_2$), 7.25 (m, 3, Ar), 8,0 ppm (m, 2, Ar); mass spectrum m/e 207 (M^+), 130 (M − C_6H_5), 105 ($ArCO^+$), 87 ($C_4H_7S^+$).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76; S, 15.47. Found: C, 63.95; H, 6.29; N, 6.41; S, 15.86.

Elution of band 2 gave 121 mg (11%) of unreacted benzamide, while bands 3 and 4 gave small amounts of impure materials. Rechromatography of the fastest band using CCl_4–acetone (94:6) gave 348 mg (17%) of benzonitrile, identified by vpc, and 285 mg of an oil that was crystallized from hexane giving 132 mg (4%) of **27**, mp 155–156°, that was identical with that from the DMSO reaction.

C. With DMSO–Phosphorus Pentoxide.—Phosphorus pentoxide (3.2 g) was slowly added with cooling to DMSO (10 ml) followed, after 20 min, by benzamide (2.42 g, 20 mmol). Colorless needles began to separate after 1 hr and after 6 hr at 23° the mixture was diluted with ethyl acetate and water, cooled, and neutralized with 1 *N* sodium hydroxide. Crystalline **31** (965 mg) was removed and the water-extracted organic phase was evaporated and dissolved in chloroform, giving a further 442 mg of crystalline **31**. The mother liquors were chromatographed on two preparative plates using CCl_4–acetone (1:1) giving three major bands. Elution of the faster band and crystallization from ether gave 212 mg (total yield 1.62 g, 61%) of *N*,*N*′-methylenebisbenzamide (**31**): mp 221–223° (lit.[29] mp 219°); λ_{max}^{MeOH} 228 mμ (ε 22,500); ν_{max} (KBr) 3280, 1635, 1525 cm^{-1}; nmr (DMSO-d_6) 4.93 (t, 2, $J_{H,NH}$ = 5 Hz, $NHCH_2NH$), 7.5 (m, 3, Ar), 8.0 (m, 2, Ar), 9.05 ppm (t, 2, J = 5 Hz, NH); mass spectrum (20 eV) m/e 254 (M^+), 149 (M − ArCO), 105 ($ArCO^+$).

Elution of the middle band gave 111 mg (5%) of unreacted **23a**, while elution of the slowest band followed by crystallization from ether gave 460 mg (13%) of **25a**, mp 108–109°, identical with that above.

D. With DMSO–Acetic Anhydride.—A solution of benzamide (2.42 g, 20 mmol) in DMSO (5 ml) and acetic anhydride (5 ml) was kept at 115° for 24 hr and then cooled, giving 740 mg of crystalline product. Addition of ether (15 ml) gave a further 140 mg (total yield 880 mg, 35%) of **31**, mp 219–220°. Recrystallization from acetone raised the melting point to 221–223°, identical with that of the material from C.

E. With DCC in DMF.—A solution of benzamide (1.21 g, 10 mmol), DCC (5 g), and anhydrous orthophosphoric acid (5 mmol) in DMF (3.5 ml) and benzene (3.5 ml) was kept for 24 hr. After addition of ethyl acetate and water (1 ml) the mixture was kept for 7 hr and filtered. The filtrate was extracted three times with water, dried, and examined by tlc using CCl_4, which showed an intense spot of benzonitrile. Quantitative glc indicated the presence of 826 mg (80%) of benzonitrile.

Photolysis of *N*-Benzoyl-*S*,*S*-dimethylsulfilimine (25a).—A solution of **25a** (362 mg, 2 mmol) in methanol (85 ml) was irradiated under argon in a quartz tube for 2 hr using a 15-W General Electric G15T8 germicidal lamp. After evaporation of the solvent, the residue was separated into three bands by preparative tlc using CCl_4–acetone (7:3). Elution of the fastest band gave 109 mg (33%) of crystalline methyl carbanilate (**37**), mp 46–47° (lit.[37] mp 47°), that was identical with an authentic sample by infrared and ultraviolet spectroscopy and by glc using a 5-ft column of 10% NPGS on Gas-Chrom Q at 155°.[46] Elution of the middle band followed by Kugelrohr distillation[45] at 90° (0.01 mm) gave 20 mg (7%) of *N*-methoxybenzamide[36] that was identical (nmr, ir, uv, and glc) with an authentic sample. The slowest band contained 112 mg (47%) of benzamide.

***N*-Methoxydibenzamide.**—Benzoyl chloride (2.2 g, 15.7 mmol) was added dropwise to a suspension of methoxylamine hydrochloride (1.3 g, 15.6 mmol) in pyridine (5 ml) and chloroform (3 ml) and the mixture was kept for 2 days. The mixture was partitioned between chloroform and 4 *N* hydrochloric acid and the organic phase was washed with water and separated into two bands by preparative tlc using CCl_4–acetone (3:2). Elution of the slower band followed by Kugelrohr distillation at 90° (0.01 mm) gave 1.39 g of *N*-methoxybenzamide:[36] λ_{max}^{MeOH} 225 mμ (ε 10,100); nmr ($CDCl_3$) 3.75 (s, 3, OCH_3), 7.39 (m, 3, Ar), 7.83 (m, 2, Ar), 11.2 ppm (br s, 1, NH). Elution of the fastest band gave 483 mg (24%) of *N*-methoxydibenzamide: mp 82–84° from hexane; λ_{max}^{MeOH} 238 mμ (ε 21,400), 252 (sh, 17,300); nmr ($CDCl_3$) 3.92 (s, 3, OMe), 7.5 (m, 8, Ar), 8.21 ppm (m, 2, Ar); mass spectrum (70 eV) m/e 255 (M^+), 105 ($ArCO^+$), 77 ($C_6H_5^+$).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.62; H, 5.22; N, 5.70.

Reaction of *N*-Benzoyl-*S*,*S*-dimethylsulfilimine with Acetic Anhydride.—A solution of **25a** (300 mg, 1.65 mmol) in acetic

anhydride (2 ml) was heated under reflux for 2 hr. After evaporation of the solvent, the residue was purified by preparative tlc using CCl_4–acetone (4:1) giving four bands. Elution of the slowest band followed by crystallization from ether–methylene chloride gave 27 mg (13%) of *N,N'*methylenebisbenzamide (**31**), mp 220–222°, identical with the sample from benzamide–DMSO–P_2O_5. Elution of the second band gave 18 mg (6%) of benzoic acid while elution of the third band and crystallization from hexane gave 117 mg (44%) of *N*-acetylbenzamide: mp 115° (lit.[31] mp 117–118°); λ_{max}^{MeOH} 233 mμ (ε 14,600); ν_{max} (KBr) 3250, 1740, 1675 cm^{-1}; nmr ($CDCl_3$) 2.57 (s, 3, $COCH_3$), 7.6 (m, 3, Ar), 8.0 (m, 2, Ar), 9.67 ppm (br s, 1, NH); mass spectrum (70 eV) *m/e* 163 (M^+), 105 ($C_6H_5CO^+$), 77 (C_6H_5). Elution of the fastest band followed by Kugelrohr distillation gave 14 mg of a slightly impure oil that was tentatively identified as *N,N*-diacetylbenzamide: nmr ($CDCl_3$) 2.37 (s, 6, NAc_2), 7.55 (m, 3, Ar), 7.90 ppm (m, 2, Ar); mass spectrum *m/e* 205 (M^+).

Reaction of 25a with Phosphoric Acid.—A solution of **25a** (300 mg, 1.65 mmol) in anhydrous DMF (1 ml) containing anhydrous orthophosphoric acid (0.15 mmol) was heated at 140° for 16 hr. Upon cooling, crystalline *N,N'*-methylenebisbenzamide (70 mg) separated. The filtrate was diluted with chloroform, extracted with 0.1 *N* sodium hydroxide, and evaporated. Crystallization from ether gave a further 65 mg (total 64%) of **31**, mp 221–223°. Preparative tlc on the mother liquors using $CHCl_3$–ethyl acetate (85:15) gave 53 mg (26%) of crystalline benzamide, mp 132–133°.

***N*-Benzoyl-*S,S*-dimethylsulfoximine (33).**—A solution of **25a** (1.15 g, 6.4 mmol) and potassium permanganate (1 g, 6.4 mmol) in water (10 ml) was heated at 100° for 10 min. Chloroform was added and after vigorous stirring the precipitated manganese dioxide was removed by filtration and washed with chloroform. Fresh chloroform was added to the aqueous phase and sulfur dioxide was bubbled through. After filtration, the combined chloroform solutions were extracted once with water, dried, and evaporated, leaving 1.18 g (95%) of crystalline material. Traces of impurities were removed by preparative tlc using CCl_4–acetone (1:1) and crystallization from water, giving 1.07 g (86%) of **33**: mp 107.5–108° (lit.[34a] mp 107–108°); λ_{max}^{MeOH} 238 mμ (ε 18,300); ν_{max} (KBr) 1612, 1575 cm^{-1}; nmr ($CDCl_3$) 3.33 (s, 6, SMe_2), 7.35 (m, 3, Ar), 8.1 ppm (m, 2, Ar); mass spectrum (15 eV) *m/e* 197 (M^+), 120 ($M - C_6H_5$), 91.

***N*-Benzoyl-*S,S*-tetramethylenesulfoximine (34).**—A solution of **32** (414 mg, 2 mmol) and potassium permanganate (330 mg) in water (5 ml) was heated at 100° for 15 min and excess permanganate was destroyed by addition of acetone followed by sulfur dioxide. After filtration and evaporation of the acetone, colorless crystals (361 mg, 81%) of **34** were obtained and could be recrystallized from water: mp 122–123° (lit.[34b] mp 121–122°); λ_{max}^{MeOH} 239 mμ (ε 18,700); ν_{max} (KBr) 1615, 1575 cm^{-1}; nmr ($CDCl_3$) 2.22 (m, 4, $S^+CH_2CH_2$), 3.4 (m, 4, SCH_2CH_2), 7.33 (m, 3, Ar), 8.05 ppm (m, 2, Ar); mass spectrum *m/e* 223 (M^+), 146 ($M - C_6H_5$), 105 ($ArCO^+$).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.40; H, 5.92; N, 6.43; S, 14.17.

Photolysis of *N*-Benzoyl-*S,S*-dimethylsulfoximine (33).—A solution of **33** (394 mg, 2 mmol) in methanol (90 ml) was irradiated under argon as with **25a** above for 18 hr, at which point glc showed the presence of essentially only benzamide and DMSO. No dimethyl sulfone was present. Preparative tlc using CCl_4–acetone (1:1) followed by crystallization from benzene gave 156 mg (65%) of benzamide, mp 132–133°, and a trace (5 mg) of an unidentified, less polar compound.

Reaction of β-Naphthylacetamide (23b).—A solution of **23b** (1.85 g, 10 mmol), DCC (4.5 g, 22 mmol), and anhydrous orthophosphoric acid (5 mmol) in DMSO (5 ml) and benzene (5 ml) was kept at 23° for 2 days. After addition of ethyl acetate and water (2 ml) the mixture was kept overnight, filtered, and extracted three times with water. The organic phase was purified by preparative tlc on four plates using ethyl acetate–methanol (7:3), giving three bands. Elution of the slowest band followed by crystallization from methylene chloride–ether gave 692 mg (28%) of *S,S*-dimethyl-*N*-(β-naphthylacetyl)sulfilimine (**25b**): mp 93–94°; λ_{max}^{MeOH} 225 mμ (ε 33,800), 268 (5700), 276 (5400), 287 (3700); ν_{max} (KBr) 1550 cm^{-1}; nmr ($CDCl_3$) 2.55 (s, 6, SMe_2), 3.77 (s, 2, $ArCH_2CO$), 7.2–8.0 ppm (m, 7, Ar); mass spectrum *m/e* 245 (M^+), 183 ($ArCH_2CO^+$), 141 ($ArCH_2^+$), 104 (Me_2SNCO).

Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.53; H, 6.16; N, 5.71; S, 13.07. Found: C, 68.58; H, 6.06; N, 5.88; S, 12.97.

Elution of the middle band gave 353 mg (19%) of unreacted **23b**, while elution of the fastest band gave 524 mg (31%) of β-naphthylacetonitrile: mp 85–86° from hexane (lit.[32] mp 85.5–86°); ν_{max} (KBr) 2250, 1600, 1510, 1410 cm^{-1}; identical with an authentic sample.

Reaction with Uracil (38a).—A solution of uracil (2.24 g, 20 mmol), DCC (11.6 g, 56 mmol), and anhydrous phosphoric acid (10 mmol) in a mixture of DMSO (20 ml) and benzene (2 ml) was kept at room temperature for 7 days.

After addition of water and ethyl acetate the solution was filtered and the organic phase was repeatedly extracted with water. Evaporation of the aqueous phase and crystallization from water gave 323 mg of unreacted uracil. Thr organic phase was separated into six bands by preparative tlc on five plates using two developments with CCl_4–acetone (3:1). Elution of the fastest band (band 1) gave a solid (270 mg, 2%) that consistently partially decomposed to **38c** during crystallization. Rechromatography using chloroform–ethyl acetate (9:1) gave **38d** as a homogeneous syrup that crystallized upon addition of ether: mp 179–180° with resolidification and decomposition above 240°; λ_{max}^{MeOH} 266 mμ (ε 8300); nmr (pyridine-d_5) 0.8–2.2 (m, 40, cyclohexyl), 4.0 (m, 4, >CHNH), 5.62 and 5.69 (s, 2, NCH_2N), 5.99 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 7.0 and 7.82 (d, 1, *J* = 8 Hz, NH), 8.27 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6 H).

Anal. Calcd for $C_{32}H_{52}N_6O_4$: C, 65.72; H, 8.96; N, 14.37. Found: C, 65.84; H, 8.69; N, 14.12.

Rechromatography of band 2 using CCl_4–acetone (3:1) removed 378 mg of a more polar decomposition product (**38b**, see below) and gave 362 mg of material which was dissolved in ether leaving some dicyclohexylurea. Crystallization of the soluble portion from ether–methylene chloride gave 157 mg (2%) of 3-(1,3-dicyclohexyl-1-ureidomethyl)-1-(methylthiomethyl)uracil (**38e**): mp 130–132°; λ_{max}^{MeOH} 270 mμ (ε 7900); ν_{max} (KBr) 3250, 1700, 1655, 1540 cm^{-1}; nmr (pyridine-d_6) 1–2.5 (m, 20, cyclohexyl), 2.20 (s, 3, SMe), 4.9 (m, 2, >CHN), 5.08 (s, 2, SCH_2N), 5.57 (s, 2, NCH_2N), 5.96 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 7.60 (d, 1, *J* = 6 Hz, NH), 7.85 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6 H); mass spectrum *m/e* 408 (M^+), 282 ($M - C_6H_{11}NCO$), 224 (DCU), 172 (CH_3SCH_2 – uracil), 125 ($C_6H_{11}NCO$).

Anal. Calcd for $C_{20}H_{32}N_4O_3S$: C, 58.79; H, 7.90; N, 13.71; S, 7.85. Found: C, 59.00; H, 7.83; N, 13.87; S, 7.91.

Band 3 contained only a small amount of an unidentified compound, while rechromatography of band 4 using chloroform–ethyl acetate (1:1) gave 207 mg (total recovery 530 mg, 24%) of uracil and a less polar product that was crystallized from methylene chloride–ether, giving 123 mg (2%) of 3-(1,3-dicyclohexyl-1-ureidomethyl)uracil (**38f**) which slowly decomposed above 150°: λ_{max}^{MeOH} 262 mμ (ε 6300); $\lambda_{max}^{pH\ 7}$ 262 mμ, $\lambda_{max}^{pH\ 12}$ 292 mμ (ε 8900), $\epsilon_{max}^{pH\ 7}/\epsilon_{max}^{pH\ 12}$ = 0.70; nmr (pyridine-d_5) 1–2.7 (m, 20, cyclohexyl), 4.0 (m, 2, >CHN), 5.60 (s, 2, NCH_2N), 5.87 (d, 1, $J_{5,6}$ = 7 Hz, C_5 H), 7.64 (d, 1, $J_{5,6}$ = 7 Hz, C_6 H), 7.91 ppm (d, 1, *J* = 7 Hz, NH).

Anal. Calcd for $C_{18}H_{28}N_4O_3$: C, 62.04; H, 8.10; N, 16.08. Found: C, 62.07; H, 8.01; N, 15.50.

Elution of band 5 and crystallization from methanol–ethyl acetate gave 718 mg (10%) of 1-(1,3-dicyclohexyl-1-ureidomethyl)uracil (**38c**) which underwent a change in crystal structure at 185–188° and decomposed without melting above 275°: λ_{max}^{MeOH} 262 mμ (ε 10,000), $\lambda_{max}^{pH\ 12}$ 265 mμ (ε 7400), $\epsilon_{max}^{pH\ 7}/\epsilon_{max}^{pH\ 12}$ = 1.35; ν_{max} (KBr) 3390, 1680, 1640, 1515 cm^{-1}; nmr (pyridine-d_5) 1–2.3 (m, 20, cyclohexyl), 3.9 (m, 2, >CHN), 5.60 (s, 2, NCH_2N) 5.86 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 6.76 (d, 1, *J* = 7 Hz, NH), 8.09 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6 H); mass spectrum *m/e* 348 (M^+), 237 (M – uracil), 125 ($C_6H_{11}NCO$), 112 (uracil).

Anal. Calcd for $C_{18}H_{28}N_4O_3$: C, 62.04; H, 8.10; N, 16.08. Found: C, 61.92; H, 7.99; N, 16.32.

Elution of band 6 followed by rechromatography using CCl_4–acetone (3:2) and rystallization from methylene chloride–ethyl acetate gave 170 mg (total yield 548 mg, 16%) of 1-(methylthiomethyl)uracil (**38b**): mp 170–171°; λ_{max}^{MeOH} 267 mμ (ε 9500), $\lambda_{max}^{pH\ 12}$ 265.5 mμ (ε 7000), $\epsilon_{max}^{pH\ 7}/\epsilon_{max}^{pH\ 12}$ = 1.35; ν_{max} (KBr) 1725, 1670, 1630 cm^{-1}; nmr (pyridine-d_5) 2.22 (s, 3, SMe), 5.05 (s, 2, NCH_2S), 5.89 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 7.65, (d, 1, $J_{5,6}$ = 8 Hz, C_6 H), 12.5 ppm (br s, 1, NH).

Anal. Calcd for $C_6H_8N_2O_2S$: C, 41.86; H, 4.68; N, 16.28; S, 18.62. Found: C, 41.68; H, 4.60; N, 16.11; S, 18.59.

Desulfurization of a sample of **38b** was effected by stirring in methanol with Davidson sponge nickel catalyst[47] for 60 hr and

(47) Davidson Chemical Division of W. R. Grace & Co., Cincinnati, Ohio.

gave a low yield of 1-methyluracil: mp 225° (lit.[40] mp 231°); $\lambda_{max}^{pH\ 7}$ 266 mμ; $\lambda_{max}^{pH\ 12}$ 264 mμ; $\epsilon_{max}^{pH\ 7}/\epsilon_{max}^{pH\ 12}$ = 1.35.

Reaction with 2′,3′,5′-Tri-*O*-benzoyluridine (39a).—A solution of **39a** (1.11 g, 2 mmol), DCC (1.24 g, 6 mmol), and anhydrous phosphoric acid (1 mmol) in DMSO (5 ml) and benzene (3 ml) was kept at room temperature for 5 days. After the usual work-up with ethyl acetate, the mixture was purified by preparative tlc using chloroform–acetone (10:1) which gave 0.51 g (46%) of unreacted uridine and a single faster band containing 0.86 g of a foam. Rechromatography of the latter using two developments with methylene chloride–ether (19:1) separated it into two components. The slower, major product (**39b**, 640 mg, 40%) was obtained as a dry, homogeneous foam: λ_{max}^{MeOH} 230 mμ (ε 42,400), 260 (13,000); nmr ($CDCl_3$) 1–2 (m, 20, cyclohexyl), 3.6 (m, 2, >CHN), 4.80 (m, 3, $C_{4'}$ H and $C_{5'}$ H), 5.37 (s, 2, NCH_2N), 5.74 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 5.85 (m, 2, $C_{2'}$ H and $C_{3'}$ H), H), 6.28 (d, 1, $J_{1',2'}$ = 4.5 Hz, C_1 H), 7.08 (d, 1, J = 7 Hz, NH), 7.5 (m, 10, Ar and C_6 H), 8.1 ppm (m, 6, Ar).

Anal. Calcd for $C_{44}H_{48}N_4O_{10}$: C, 66.65; H, 6.10; N. 7.07. Found: C, 66.16; H, 6.07; N, 6.84.

Elution of the faster band gave **39c** (118 mg, 10%) as a homogeneous froth: λ_{max}^{MeOH} 229 mμ (ε 38,700), 258 (10,800); ν_{max} (KBr) 1735, 1675 cm^{-1}; nmr ($CDCl_3$) 2.19 (s, 3, SMe), 4.7 (m, 3, $C_{4'}$ H, $C_{5'}$ H_2), 4.86 and 5.02 (d, 1, J_{gem} = 13 Hz, NCH_2S), 5.65 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 5.8 (m, 2, $C_{2'}$ H and $C_{3'}$ H), 6.27 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}$ H), 7.36 (d, 1, $J_{5,6}$ = 8 Hz, C_6 H), 7.3–8.2 ppm (m, 15, Ar).

Anal. Calcd for $C_{32}H_{28}N_2O_9S$: C, 62.35; H, 4.58; N, 4.54. Found: C, 62.30; H, 4.62; N, 4.24.

Reaction with Phthalimide (40a).—Phthalimide (2.21 g, 15 mmol), DCC (8.7 g), and anhydrous phosphoric acid (7.5 mmol) reacted in DMSO (7.5 ml) and benzene (7.5 ml) for 2 days and worked up in the usual way with ethyl acetate. Direct crystallization of the residue from methanol gave 880 mg (40%) of unreacted **40a**, and chromatography of the mother liquors on three preparative plates using CCl_4–acetone (9:1) gave two bands in addition to a further trace (52 mg) of **40a**. Elution of the faster band gave 1.16 g (38%) of *N*-(methylthiomethyl)phthalimide (**40b**): mp 112.5–113.5° from hexane; λ_{max}^{MeOH} 218 mμ (ε 20,000), 295 (1700); ν_{max} (KBr) 1760, 1700, 1615 cm^{-1}; nmr ($CDCl_3$) 2.26 (s, 3, SMe) 4.75 (s, 2, NCH_2S), 7.80 ppm (m, 4, Ar).

Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76; S, 15.36. Found: C, 58.16; H, 4.38; N, 6.85; S, 15.36.

Elution of the slower band gave 512 mg of a crystalline mixture of two compounds, one being nonultraviolet absorbing. Fractional crystallization from hexane gave 121 mg (2%) of pure 2-(1,3-dicyclohexyl-1-ureidomethyl)phthalimide (**40c**): mp 146–148°; λ_{max}^{MeOH} 217 mμ (ε 42,500), 296 (2200); ν_{max} (KBr) 3360, 1780, 1720, 1660 cm^{-1}; nmr ($CDCl_3$) 1.0–2.25 (m, 20, cyclohexyl), 3.75 (m, 2, >CHN), 5.10 (s, 2, NCH_2N), 6.70 (d, 1, J = 7 Hz, NH), 7.83 ppm (s, 4, Ar); mass spectrum *m/e* 383 (M^+), 301 (M − C_6H_{10}), 258 (M − $C_6H_{11}NCO$), 223 [$C_6H_{11}N(C{=}O)NHC_6H_{11}^+$], 160 (M − 223).

Anal. Calcd for $C_{22}H_{29}N_3O_3$: C, 68.90; H, 7.62; N, 10.96. Found: C, 69.30; H, 7.72; N, 11.31.

Desulfurization of 40b.—A solution of **40b** (200 mg) in methanol (25 ml) was stirred for 20 hr with about 0.5 g of Davidson sponge nickel.[48] The mixture was filtered and the nickel was washed with hot methanol (300 ml). Evaporation of the combined filtrates left 117 mg of a crystalline residue which was crystallized from ether–hexane, giving 90 mg (58%) of *N*-methylphthalimide (**40e**): mp 132–134° (lit.[42] mp 133.5–134°); λ_{max}^{MeOH} 217 mμ (ε 40,700), 231 (16,500), 239 (12,200); nmr ($CDCl_3$) 3.15 (s, 3, NMe), 7.76 ppm (m, 4, Ar).

***N*-(Methylthiomethoxy)phthalimide (41b).**—A solution of *N*-hydroxyphthalimide (1.63 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (10 ml) and benzene (10 ml) was kept for 3 hr at 23°. After dilution with ether, the mixture was filtered and the filtrate was extracted theee times with water, dried, and evaporated. The residue was chromatographed on a column of silicic acid using benzene–chloroform (1:3) giving 1.29 g (58%) of crystalline product. Recrystallization from hexane gave 1.17 g (53%) of **41b**: mp 102–103°; λ_{max}^{MeOH} 219 mμ (ε 29,000), 237 (sh, 9000), 294 (1500); ν_{max} (KBr) 1790, 1735 cm^{-1}; nmr ($CDCl_3$) 2.38 (s, 3, SMe), 5.20 (s, 2, OCH_2S), 7.82 ppm (s, 4, Ar); mass spectrum *m/e* 223 (M^+), 61 ($CH_2{=}SCH_3$).

Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.28; S, 14.35. Found: C, 53.94; H, 4.20; N, 6.27; S, 14.50.

Reactions with Isatin (42a).—A mixture of isatin (2.21 g, 15 mmol), DCC (7 g, 34 mmol), and anhydrous phosphoric acid (7.5 mmol) in DMSO (10 ml) and benzene (5 ml) was kept for 5 days and then worked up as usual with ethyl acetate. Preparative tlc using two developments with CCl_4–acetone (9:1) gave unreacted isatin (1.22 g, 55%) and two faster bands. The slower of these (389 mg) contained a mixture of products and was not further investigated. Elution of the faster band and crystallization from ether gave 1.35 g (24%) of red *N*-(1,3-dicyclohexyl-1-ureidomethyl)isatin (**42b**): mp 158–159°; λ_{max}^{MeOH} 208 mμ (ε 18,700), 243 (15,700), 250 (13,700), 396 (2400), 425 (370); ν_{max} (KBr) 3450, 1715, 1645, 1615 cm^{-1}; nmr ($CDCl_3$) 1–2.2 (m, 20, cyclohexyl), 3.5 (m, 2, >CHN), 5.21 (d, 1, J = 7 Hz, NH), 5.46 (s, 2, NCH_2N), 7.15 (m, 1, Ar), 7.55 ppm (m, 3, Ar); mass spectrum *m/e* 383 (M^+), 258 (M − $C_6H_{11}NCO$), 237 (M − phthalimide), 147 (M − 237), 112 ($C_6H_{11}NH{=}CH_2$).

Anal. Calcd for $C_{22}H_{29}N_3O_3$: C, 68.90; H, 7.62; N, 10.96. Found: C, 68.80; H, 7.92; N, 10.84.

Elution of a small, partially resolved band at the front of the fast band gave, after crystallization from ether–methylene chloride, 32 mg (1%) of orange *N*-(methylthiomethyl)isatin (**42c**): mp 128–129°; ν_{max} (KBr) 1730, 1615 cm^{-1}; nmr ($CDCl_3$) 2.16 (s, 3, SMe), 4.84 (s, 2, NCH_2S), 7.16 (m, 2, Ar), 7.67 ppm (m, 2, Ar); mass spectrum *m/e* 207 (M^+), 160 (M − SCH_3), 146 (M − CH_3SCH_2), 132 (M − CH_3SCH_2N).

Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.63; H, 4.69; N, 6.91.

Registry No.—**5a,** 5388-04-5; **5b,** 31280-16-7; **7a,** 14908-53-3; **7b,** 31280-18-9; **12,** 6744-64-5; **13,** 31280-20-3; **14,** 1613-79-2; **15,** 31280-22-5; **16a,** 31280-23-6; **16b,** 31280-24-7; **17a,** 31280-25-8; **17b,** 31280-26-9; **25a,** 19397-91-2; **25b,** 31280-28-1; **26,** 31280-29-2; **27,** 6074-63-1; **31,** 1575-94-6; **32,** 31280-32-7; **33,** 31280-33-8; **34,** 3532-35-2; **38b,** 31280-35-0; **38c,** 31280-36-1; **38d,** 31280-37-2; **38e,** 31280-38-3; **38f,** 31280-39-4; **39b,** 31280-40-7; **39c,** 31280-41-8; **40b,** 20044-28-4; **40c,** 31280-43-0; **40e,** 550-44-7; **41b,** 31280-44-1; **42b,** 31280-45-2; **42c,** 20044-27-3; benzamidodimethylsulfonium chloride, 31280-46-3; *N*-methoxydibenzamide, 31280-47-4; *N*-methoxybenzamide, 2446-51-7; *N*-acetylbenzamide, 1575-95-7.

Steric Hindrance in a Cis-Trisubstituted Cyclopropane Derivative. Molecular Structure of 1-Chloro-1-phenylsulfonyl-2,3-dimethylcyclopropane

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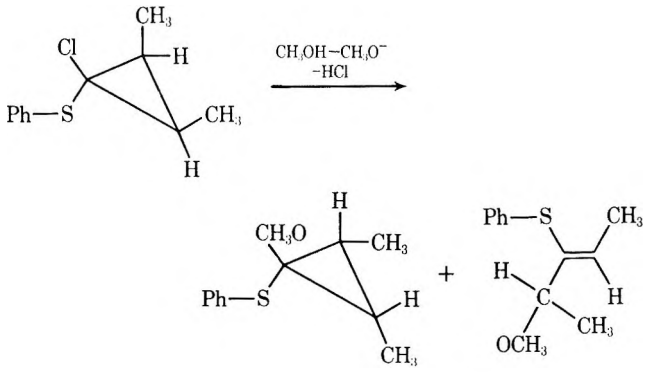
The methanolysis of 1-chloro-1-phenylmercapto-2,3-dimethylcyclopropane suggested the presence of a cyclopropyl cation as intermediate. Since the configuration of the reagent was unknown, it was oxidized to yield the sulfone and the crystals of triclinic space group $P\bar{1}$ were investigated by X-ray analysis. The structure was solved by the heavy atom method and refined to $R = 5.7\%$. The geometry of the cyclopropyl residue exhibits several features characteristic for these structures such as shortening of endocyclic C–C and exocyclic C–Cl, C–S, C–C bond distances. There is considerable steric hindrance between the cis substituents of the cyclopropyl residue, and the conformation about the S–C(1) bond is such that O(2) is "above" the triangle.

When 1-chloro-1-phenylmercapto-2,3-dimethylcyclopropane was subjected to methanolysis, a cyclic and an open chain reaction product was obtained. This finding was interpreted on the assumption that due to the



stabilizing +M effect of the sulfur atom a cyclopropyl cation was present as a reaction intermediate.[1] The knowledge of the configuration of 1-chloro-1-phenylmercapto-2,3-dimethylcyclopropane was essential for the deduction of the reaction mechanism. However, the structure of the liquid reagent could not be established unambiguously by chemical or spectroscopic means and so it was oxidized to yield the crystalline 1-chloro-1-phenylsulfonyl-2,3-dimethylcyclopropane (I) and investigated in the X-ray structural analysis described below.

Materials and Methods.—We obtained I from U. Schöllkopf and P. Tonne in the form of stout plates crystallized from decalin (mp 93°). The crystallographic data presented in Table I were gathered from

TABLE I

CRYSTALLOGRAPHIC DATA

Space group triclinic, $P\bar{1}$

$a = 7.891 \pm 0.002$ Å	$\alpha = 91.23 \pm 0.02°$
$b = 10.608 \pm 0.003$ Å	$\beta = 111.29 \pm 0.02°$
$c = 7.801 \pm 0.002$ Å	$\gamma = 100.81 \pm 0.02°$

Chemical formula, $C_{11}H_{13}ClO_2S$
Molecular weight, 244.75
Density observed (flotation in $KI-H_2O$), 1.354 g/cm³
Density calculated (with $Z = 2$), 1.366 g/cm³
Linear absorption coefficient (Mo), $\mu = 4.7$ cm⁻¹
Dimensions of crystal, 0.2 × 0.1 × 0.4 mm

photographic and diffractometer measurements. The 2110 intensity data were collected by H. A. Paulus (Darmstadt) on an automatic STOE four-circle diffractometer using graphite monochromatized Mo radition. The data were corrected for the usual geometrical factors and for the extra polarization caused by the monochromator[2] ($2\theta_M = 12°$). Due to the smallness of the crystal and of the linear absorption coefficient an absorption or extinction correction was deemed unnecessary.

From these data we calculated normalized structure factors (E's).[3] The mean $\langle E \rangle$ of 0.80 and mean $\langle E^2 - 1 \rangle$ of 0.93 suggested a centrosymmetric structure as did the distribution of E magnitudes.[4] A sharpened, origin-reduced Patterson map was prepared with ($E^2 - 0.95$) as coefficients, from which we could determine the locations of the "heavy" atoms S and Cl. A minimum function superposition[5] based on these atomic positions and their inversion-related mates revealed all atoms except phenyl ring carbon atoms C(9) and C(10) which could be found in a subsequent Fourier synthesis. A structure factor calculation based on positions for all nonhydrogen atoms from the electron density map and isotropic temperature ($B = 3.8$ Å²) and a scale factor from a Wilson[6] plot yielded a reliability index $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.28$. Full matrix least-squares refinement[7] of coordinates, scale, and isotropic temperature factors reduced R to 0.113.

In the course of the refinement the quantity minimized was $\Sigma W_{F_o}(|F_o| - |F_c|)^2$ where W_{F_o} means a weight to consider random and determinate errors of counting;[8] 252 reflections with $F_o < 3/\sqrt{W_{F_o}}$ were treated as unobserved.[8]

All hydrogen atoms could be found at heights 0.19–0.34 e/Å³ in a difference electron density map following refinement with anisotropic temperature factors to $R = 0.072$. Refinement until shifts were less than $^1/_3$ the estimated standard deviations for all parameters including hydrogen atoms with fixed isotropic temperature factors (those of the covalently attached nonhydrogen atoms) lowered R to 0.057 for all 2110 reflections and left residuals no higher than 0.12 e/Å³ in a difference Fourier synthesis.

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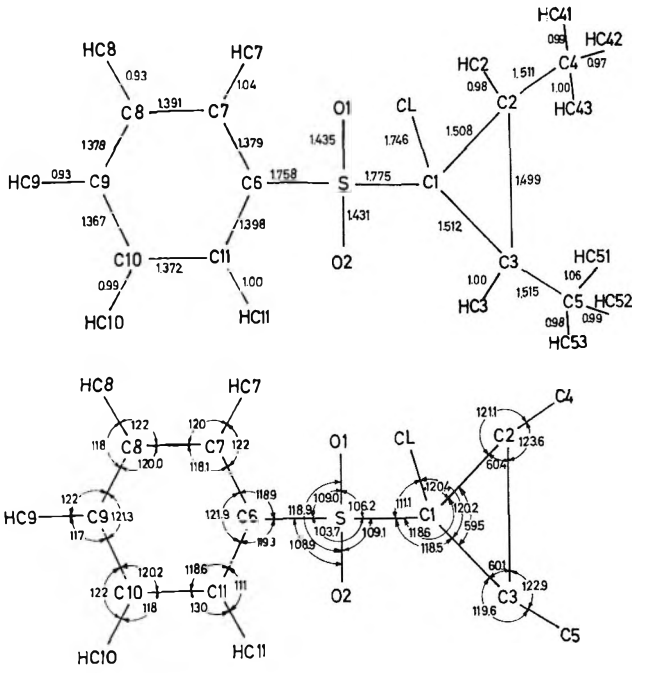

Figure 1.—Intramolecular distances and angles. The estimated standard deviations σ are 0.003 Å for distances involving S and Cl and 0.005 Å and 0.3°, respectively, for other data not involving hydrogen atoms. Distances and angles involving hydrogen atoms are accurate to about 0.05 Å and 5°, respectively. Due to the smallness of the anisotropic thermal parameters, the bond distances were not corrected for vibration effects. The bond angles C–C–HC(2) and C–C–HC(3) are 114 ± 2° while in the methyl groups bond angles C–C–H and H–C–H are 112 ± 3 and 108 ± 5°, respectively.

Results and Discussion

The final atomic parameters and the observed and calculated structure factors have been deposited with the ACS microfilm edition,[9] together with a stereoview of the packing of the molecules within the unit cell. In Figure 1 we have presented intramolecular bond distances and angles (the standard deviations are described in the legend) and in Tables II and III we have collected some least-squares planes through parts of the molecule and dihedral angles which were necessary to describe its conformation. Figure 2 shows a stereoview of a molecule when looking down b^*.

The six carbon atoms comprising the phenyl ring and the sulfur atom are nearly coplanar (Table II). The aromatic C–C bond distances should be about 1.394 Å,[10] but they are in the range from 1.367 to 1.398 Å (Figure 1) which might be due to steric and packing effects.

The C–C bond distances in the cyclopropyl residue of I are considerably shorter than paraffinic C–C single bonds (Table IV) and the C–C–C angles are close to 60°. Similar results have been predicted from theoretical consideration[11–13] and were obtained experimentally.[14–17]

(9) Listings of structure factors, coordinates, and anisotropic temperature factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

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Table II

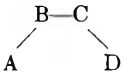
Some Least-Squares Planes in the Form $pX + qY + rZ + s = 0$[a,b]

	Plane coefficients	Atoms	Deviations of atoms from the plane
a	$p = -0.1947$	C(6) +	0.001
	$q = -0.5018$	C(7) +	0.004
	$r = 0.8428$	C(8) +	−0.007
	$s = -0.2975$	C(9) +	0.003
		C(10) +	0.002
		C(11) +	−0.004
		S	−0.016
b	$p = 0.3099$	C(1) +	0.0
	$q = 0.6857$	C(2) +	0.0
	$r = 0.6586$	C(3) +	0.0
	$s = -1.4660$	Cl	1.421
		C(4)	1.185
		C(5)	1.211
		S	−1.482
		HC(2)	−0.867
		HC(3)	−0.871
		O(1)	−2.573
c	$p = -0.9485$	Cl +	0.0
	$q = 0.2704$	C(1) +	0.0
	$r = -0.1648$	S +	0.0
	$s = -2.3019$	C(2)	0.742
		C(3)	−0.757
		C(4)	1.577
		C(5)	−1.580
		HC(2)	1.128
		HC(3)	−1.203
		O(1)	0.067
		O(2)	−1.088

[a] X, Y, Z are the atomic coordinates in Å transformed into an orthogonal system with X perpendicular to b^* and c, Y along b^*, and Z along c. Atoms which define the planes are marked +. [b] The angles between the normals to the planes are $<a,b = 16$, $<a,c = 95$, $<b,c = 90°$.

Table III

Dihedral Angles[a]



Angle	Deg	Angle	Deg
Cl–C(1)–C(2)–C(3)	109.4	O(1)–S–C(1)–C(2)	−31.3
Cl–C(1)–C(3)–C(2)	−109.7	O(1)–S–C(1)–C(3)	37.5
Cl–C(1)–C(2)–C(4)	4.3	O(1)–S–C(6)–C(7)	−36.2
Cl–C(1)–C(3)–C(5)	−3.4	O(2)–S–C(6)–C(7)	−167.3
C(4)–C(2)–C(3)–C(1)	109.6	C(1)–S–C(6)–C(7)	103.4
C(5)–C(3)–C(1)–C(2)	−108.0	S–C(1)–C(2)–C(3)	−108.0
C(4)–C(2)–C(3)–C(5)	1.7	S–C(1)–C(3)–C(2)	108.3
HC(2)–C(2)–C(3)–HC(3)	−1.2	S–C(1)–C(2)–C(4)	138.4
S–C(1)–C(2)–HC(2)	3.7	S–C(1)–C(3)–C(5)	−138.6
S–C(1)–C(3)–HC(3)	−0.6	Cl–C(1)–C(2)–HC(2)	−146.3
O(1)–S–C(1)–Cl	−177.2	Cl–C(1)–C(3)–HC(3)	142.6
O(2)–S–C(1)–Cl	−53.6		

[a] These four-atom angles are defined as zero when, looking along B → C bond B → A is parallel to bond C → D and is counted positive when C → D is rotated clockwise with respect to B → A.

In Table IV the exocyclic C(1)–Cl, C(1)–S, C(2)–C(4), and C(3)–C(5) bond distances are compared with data for the corresponding single and double bonds.

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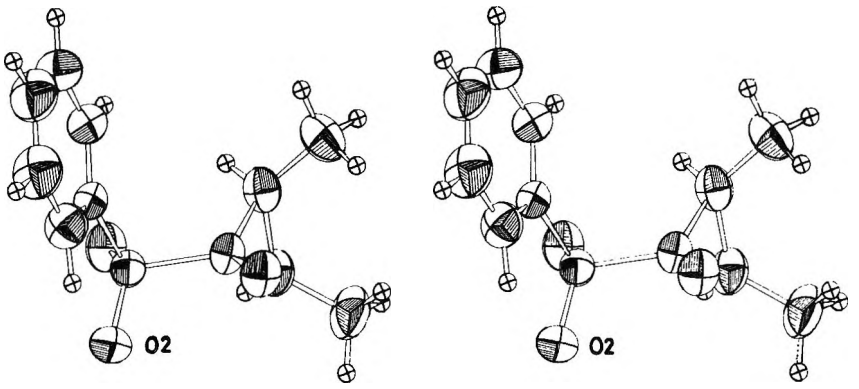

Figure 2.—A stereo plot of one molecule viewed down b^* with the 50% thermal ellipsoids: C. K. Johnson, Oak Ridge National Laboratory Report BRNL-3794, Oak Ridge, Tenn., 1965.

TABLE IV

COMPARISON OF BOND DISTANCES (IN Å) FROM THIS STRUCTURE WITH AVERAGED DATA FOR CORRESPONDING LENGTHS INVOLVING SINGLY AND DOUBLY BONDED CARBON ATOMS[a]

Data in this structure for	Averaged data	
C–Cl = 1.746	R–C–Cl = 1.767 ± 0.005	R=C—Cl = 1.719 ± 0.005
$C-CH_3$ = 1.511	$R-C-CH_3$ = 1.537 ± 0.005	$R=C-CH_3$ = 1.510 ± 0.005
$C(1)-SO_2$ = 1.775	$R-C-SO_2$ = 1.80 ± 0.01	
$C_6H_5SO_2$ = 1.758		$C_6H_5SO_2$ = 1.753 ± 0.002[b]
C(1)–C(2), C(1)–C(3) = 1.510	C–C aliph = 1.537 ± 0.005	>C=C< olefin = 1.335 ± 0.005
C(2)–C(3) = 1.499		
C–C arom = 1.367–1.398		C–C arom = 1.394 ± 0.005

[a] See ref 9. [b] See ref 22.

The bond lengths in I are between the values given in Table IV and suggest the "olefinic"[18] character of the cyclopropyl residue as do the exocyclic angles which according to the above-cited theoretical and experimental publications should be about 116° for C–C–H and about 118° for C–C–X; the angles S–C(1)–C(2), S–C(1)–C(3), and the C–C–HC(2) and C–C–HC(3) angles are close to these values. However, the angles C–C–X where X stands for the chlorine atom or the methyl groups, which are cis to each other, are significantly (7–15σ) greater than 118° and one must conclude that between these groups steric hindrance occurs. This finding is supported by the observation that the angles C(2)–C(3)–C(5) and C(3)–C(2)–C(4) are increased by 3° compared to the angles C(1)–C(3)–C(5) and C(1)–C(2)–C(4) (Figure 1) which can be interpreted in terms of the greater van der Waals[20] radius of the methyl group (2.0 Å) with respect to the chlorine atom (1.8 Å). Another indication for steric hindrance are the interatomic, nonbonded distances Cl–C(4), 3.173 Å, Cl–C(5), 3.145 Å, C(4)–C(5), 3.029 Å, which all are smaller than the corresponding sum of the van der Waals radii, 3.8 Å for $Cl-CH_3$ and 4 Å for CH_3-CH_3, respectively.

It must be due to the symmetry of the cyclopropyl residue—the plane Cl–C(1)–S acts as a pseudo mirror plane (Table II)—that in spite of the just mentioned steric hindrance its substituents are truly cis to each other; *i.e.*, in the four-atom planes Cl, C(1), C(2), C(4); Cl, C(1), C(3), C(5); C(4), C(2), C(3), C(5) the atoms are coplanar with maximum discrepancies of 0.02 Å; the angles between the normals to these planes are about 70°.

The angle Cl–C(1)–S of 111.1° is smaller than the expected value of 116–118°. A similar angle was found for Cl–C–Cl (114°) in 1,1-dichlorocyclopropane[17] and for O–C–O (110°) in benzocyclopropapyran.[21]

Bond angles and distances of the sulfonyl group compare well with data obtained for saccharine derivatives[22,23] and for *N*-methyl-2-methylsulfonyl-2-phenylsulfonylvinylideneamine.[24]

The conformation of I is such that the S–O(2) bond is almost coplanar with the phenyl ring [Table III; the O(2)–S–C(6)–C(7) dihedral angle is only 13°] while the S–O(1) bond is almost cis planar with the cyclopropyl residue; *i.e.*, the projection of the S–O(1) bond along the S–C(1) direction bisects the cyclopropyl triangle (Figure 2, Table III). As a consequence of this conformation the planes through phenyl and cyclopropyl residues are almost parallel to each other with an angle of only 17° between the normals to these planes.

The S–O part of a sulfonyl group can be compared to a carbonyl C–O group. It is striking that several cyclopropane derivatives with an α-carbonyl group which have been studied by electron diffraction and X-ray crystallography all exhibit a conformation similar to I: the carbonyl or S–O group, respectively,

(18) We have called the cyclopropyl residue "olefinic" referring to the π-electron picture proposed by Walsh[13] and to its chemical properties reviewed by Pete.[19]

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is cis to the cyclopropyl residue; *i.e.*, the oxygen atom is "above" the triangle. From the substances investigated by electron diffraction (cyclopropanecarboxylic acid chloride, cyclopropyl methyl ketone,[25] and cyclopropylcarboxaldehyde[26]) only average C–C distances were obtained, whereas the X-ray data for cyclopropanecarbohydrazide[27] and cyclopropanecarboxamide[28] yielded an asymmetry in the cyclopropyl residue; the C–C bond opposite the carbonyl group [*i.e.*, C(2)–C(3)] was found to be significantly (3.5 σ) smaller than the other two C–C bonds in the cyclopropyl ring which is also true (3 σ) for I, Figure 1. That the C(2)–C(3) bond distance in I is not so short as in the above two cyclopropane derivatives might be due to the steric hindrance between the C(4) and C(5) methyl groups discussed earlier.

Within the crystal structure the molecules are arranged such that the methyl groups come together in a region parallel to the *a,b* plane at $c = 1/2$ and the phenyl rings are not stacked but alternately packed around the *a,b* plane in $c = 0$.

The intermolecular distances are all equal to or greater than the sums of the corresponding van der Waals radii. Relatively close contacts occur between the chlorine atoms, 3.378 Å, and between O(1) and HC(7), 2.506 Å.

The calculations were performed on a UNIVAC 1108 computer of the Gesellschaft für wissenschaftliche Datenverarbeitung mbH, Göttingen. The ORTEP plots were carried out at Deutsches Rechenzentrum, Darmstadt.

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The Condensation of Succinic Anhydrides with Schiff Bases. Scope and Mechanism[1a]

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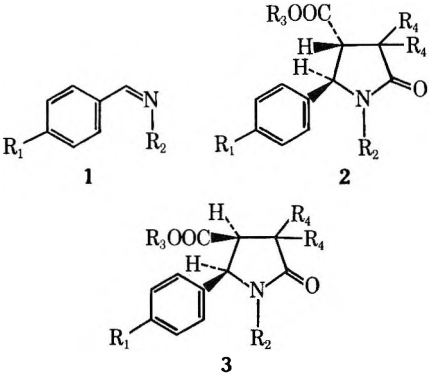
The condensation of a series of para-substituted benzylidenecyclohexylamines with succinic anhydride to yield the corresponding *trans*- and *cis*-1-cyclohexyl-4-carboxy-5-aryl-2-pyrrolidinones has been studied. The reactivities of the Schiff bases have been shown to increase with the increasing electron-donating ability of substituents, an order of reactivity opposite to that expected for a Perkin-type mechanism. Indirect evidence supporting a reaction sequence involving iminolysis of *gem*-dimethylsuccinic anhydride followed by rearrangement of the iminolysis adduct is also presented.

In a recent publication[2] we described the condensation of benzylidenemethylamine **1a** with succinic anhydride to yield *trans*- and *cis*-1-methyl-4-carboxy-5-phenyl-2-pyrrolidinone (**2a** and **3a**, respectively). In order to examine the mechanism of this reaction and concomitantly to extend its synthetic utility to the preparation of substituted 5-aryl-2-pyrrolidinones of interest as precursors to nicotine analogs,[3] we have studied the condensation of the para-substituted benzylidenecyclohexylamines **1b–f** with succinic anhydride. With the exception of the para nitro compound **1f**, which resisted reaction, each Schiff base yielded a diastereomeric mixture of pyrrolidinones which could be separated into the trans and cis isomers **2** and **3**, respectively. The cis acids **3b** and **3c** were characterized as their methyl esters **3b′** and **3c′**, respectively.

As previously shown,[2] stereochemical assignments in each case could be made on the basis of the magnitude of the coupling constant for the C-5 methine proton, which for the cis isomers is 9 Hz and for the trans isomers 2–5 Hz. Since the nmr signals for the methoxycarbonyl protons in the corresponding cis methyl esters appear about 0.4–0.5 ppm upfield from the trans esters,[2] it was possible to estimate the relative yields of the diastereomers by integration of the nmr spectra of the



1 **2** **3**

Compd	R_1	R_2	R_3	R_4
a	H	CH_3	H	H
b	$(CH_3)_2N$	C_6H_{11}	H	H
b′	$(CH_3)_2N$	C_6H_{11}	CH_3	H
c	CH_3O	C_6H_{11}	H	H
c′	CH_3O	C_6H_{11}	CH_3	H
d	H	C_6H_{11}	H	H
e	Cl	C_6H_{11}	H	H
f	NO_2	C_6H_{11}	H	H
g	CH_3O	C_6H_{11}	H	CH_3
g′	CH_3O	C_6H_{11}	CH_3	CH_3

(1) (a) Presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., 1969; (b) NDEA Predoctoral Fellow and American Foundation for Pharmaceutical Education Fellow.
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mixture of esters obtained by diazomethane treatment of the crude carboxylic acid products. The pertinent analytical and physical data for these compounds are recorded in Table I.

TABLE I

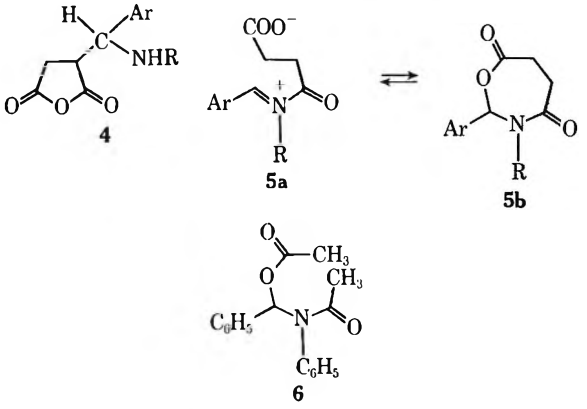
PHYSICAL AND ANALYTICAL DATA FOR 1-CYCLOHEXYL-4-CARBOXY-5-ARYL-2-PYRROLIDINONES[a]

Compd	Mp, °C	Reaction solvent (time, hr)	Crystn solvent	Yield,[b] %
2b	226–227		MeOH	37
		C_6H_6 (12)		
3b′	164–165		Me_2CO	3[c]
2c	217–218		MeOH	75
		C_6H_6 (12)		
3c′	127–128		Me_2CO–H_2O	10[c]
2d	167–168		50% EtOH	68
		C_6H_6 (24)		
3d	252–253		95% EtOH	7
2e	164–165		50% MeOH	63
		Xylene (24)		
3e	254–255		Me_2CO	8

[a] Satisfactory analytical data (±0.35% for C, H, and N) were reported for all compounds in the table: Ed. [b] Calculated from total yields of diastereomeric acids and per cent composition determined by nmr of methyl esters. [c] Refers to yield of cis acid.

Mechanistically this reaction can be viewed as proceeding in a manner analogous to the base-catalyzed Perkin condensation,[4] in which case product formation would be expected to proceed *via* the adduct **4**. An alternative proposal invokes rearrangement of the iminolysis adduct **5a** ⇄ **5b**, the formation of which finds analogy in the benzylideneaniline–acetic anhydride condensation product, **6**.[5] Ogata and Tsuchida[6] have demonstrated that the base-catalyzed Perkin condensation of acetic anhydride with substituted benzaldehydes proceeds more readily the greater the electronegativity of the aromatic substituent. In contrast to these effects, an electron-donating substituent would be expectd to facilitate the iminolysis reaction through the increased nucleophilicity of the Schiff base and increased ability to stabilize the positive charge developed during formation of **5a**. In dimethylacetamide the 60-MHz nmr signals for the methine protons of imines **1b–f** appear as singlets near 8.2 ppm and the doublets of the C-5 methine protons of the pyrrolidinones are centered near 5 ppm. Since no other signals for reactants or products occur in these regions, it was possible to follow the course of the reaction by nmr and to examine substituent effects on the reactivity of the imines.

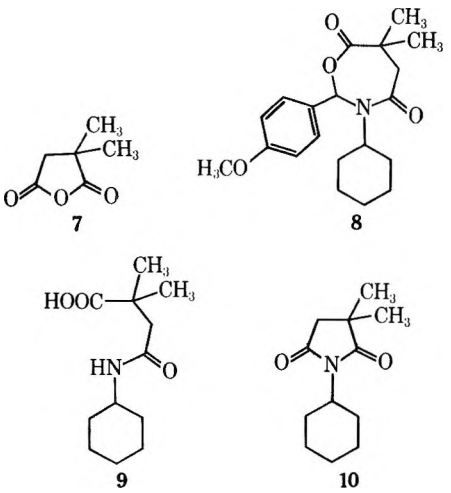
Equimolar solutions (0.1 *M*) of the imines and succinic anhydride in dimethylacetamide were heated at 100° in sealed nmr tubes for specified time periods. After the reactions were quenched by cooling to 0°, the nmr spectra were recorded at ambient temperature. The per cent imine remaining *vs.* time was plotted and the 50% reaction time was determined. Based on these values, the relative reactivities of the imines are as follows: **1b**:**1c**:**1d**:**1e**:**1f** = 100:22:5:5:<1. The same order of reactivities in terms of product formation was also observed. Furthermore, the addition of triethylamine to the benzylidenecyclohexylamine reaction mixture in concentrations known to catalyze the Perkin condensation[6] had no effect on the reaction rate, indicating that the observed order of reactivity was not a consequence of the capability of the imine to deprotonate the anhydride. These data make untenable a Perkin-type mechanism but are consistent with a mechanism involving iminolysis of the anhydride.



4 **5a** **5b**

6

The condensation of *p*-methoxybenzylidenecyclohexylamine (**1c**) with *gem*-dimethylsuccinic anhydride (**7**) was studied in an effort to isolate the adduct **8**. When run in benzene the reaction yielded the succinamic acid **9**, which was also obtained in 98% yield by aminolysis of **7** with cyclohexylamine. The same reaction was attempted in refluxing xylene and the mixture was worked up by distillation. The distillation residue gave a low yield of the trans and cis pyrrolidinones **2g** and **3g**. The coupling constants of the C-5 methine proton doublets for these two diastereomers were too similar to allow stereochemical assignments. However, the nmr spectra of their corresponding methyl esters **2g′** and **3g′** displayed the anticipated[2] differences in shifts for the methoxycarbonyl proton signals. The distillate yielded two additional compounds which by glpc were shown to be present in equal quantities. The more volatile of these two compounds proved to be *p*-methoxybenzaldehyde, which was identified by glpc retention time and nmr after isolation *via* the bisulfite addition product. The second compound was shown to be 1-cyclohexyl-3,3-dimethylsuccinimide (**10**) by nmr and microanalysis. While these results can be rationalized in terms of the iminolysis mechanism, more definitive support for the postulated intermediate is being sought.



7 **8** **9** **10**

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Experimental Section[7]

General Procedure for the Synthesis of Schiff Bases.—The aldehyde (0.3 mol) and cyclohexylamine (0.3 mol) in 100 ml of C_6H_6 were heated under reflux for 2 hr, during which time 5.4 ml (0.3 mol) of H_2O was collected in the Dean–Stark trap. After removal of the solvent, the imines were obtained pure in about 90% yield by distillation or sublimation: **1b**, mp 81–82° (*Anal.* Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.28; H, 9.64; N, 12.12); **1c**, mp 32–33° (lit.[8] mp 12°); **1d**, bp 110–120° (2 mm) [lit.[9] bp 83–85° (0.08 mm)]; **1e**, mp 53–54° (lit.[10] mp 57–58°); **1f**, mp 84–85° (lit.[11] mp 85–86°).

***trans*- and *cis*-1-Cyclohexyl-4-carboxy-5-aryl-2-pyrrolidinones.**—The imines **1b–f** (0.1 mol) and succinic anhydride (0.1 mol) in 100 ml of anhydrous C_6H_6 or xylene were heated under reflux for the times given in Table I. After cooling to room temperature the solid which formed was collected. In the case of the para chloro system, **e**, the gel which formed was extracted with aqueous $NaHCO_3$ and the acids were precipitated at pH 2 with HCl. Separations of the diastereomers were achieved as follows. The trans acids **2b–d** were obtained by crystallization of the above solids from the solvents listed in Table I. In each case, elemental analyses, sharp melting points, and the appearance of a doublet in the nmr at $\delta \sim 5$ ppm with $J = 2$–3 Hz characteristic for the trans C-5 methine signal, established the purity of the product. The cis acid of the *p*-dimethylamino compound **3b** was isolated as its Me ester (**3b′**) by treating the residue obtained from the mother liquors after crystallization of the trans acid with 0.2 *M* methanolic sulfuric acid in the presence of molecular sieves at room temperature for 18 hr. After filtering, the resulting solution in $CHCl_3$ was washed with H_2O and twice with 5% aqueous $NaHCO_3$ and then dried ($MgSO_4$). The residue obtained after removing solvent was crystallized twice from Me_2CO to yield pure **3b′**. The cis acid of the para methoxy compound **3c** was also purified as its Me ester **3c′** by treating the residue obtained from the mother liquors after crystallization of the trans acid with an excess of diazomethane in EtOH–Et_2O. The reaction mixture in $CHCl_3$ was extracted twice with 5% aqueous $NaHCO_3$ and dried ($MgSO_4$), and the residue obtained after removing the solvent was crystallized from Me_2CO and then Me_2CO–H_2O. The cis acid of the unsubstituted system (**3d**) was obtained directly by concentrating the MeOH filtrate from crystallization of the trans acid. Recrystallization from EtOH provided the analytical sample. The cis acid of the para chloro system (**3e**) was obtained by treating the mother liquor residue from the trans acid crystallization with 50% aqueous Me_2CO and recrystallizing the resulting solid from Me_2CO. The purities of the above compounds were confirmed by elemental analyses, sharp melting points, and the appearance of a doublet at $\delta \sim 5$ ppm ($J = 9$ Hz) in the nmr spectrum characteristic for the cis C-5 methine proton.

Estimation of Relative Yields of Cis and Trans Acids.—Samples (0.5 g) of the diastereomeric mixtures were methylated by addition of an excess of diazomethane in EtOH–Et_2O. The nmr spectra in $CDCl_3$ of the oil obtained after removing the solvent displayed a singlet near 3.65 ppm for the methoxycarbonyl protons of the trans esters and a second singlet near 3.25 ppm for the methoxycarbonyl protons of the cis esters. Integration of these signals provided an estimation of the relative amounts of the trans and cis acids.

Reaction of *gem*-Dimethylsuccinic Anhydride with *p*-Methoxybenzylidenecyclohexylamine. A. In C_6H_6.—*p*-Methoxybenzylidenecyclohexylamine (**1c**, 10.86 g, 0.05 mol) and *gem*-dimethylsuccinic anhydride[12] (7, 6.40 g, 0.05 mol) in 100 ml of anhydrous C_6H_6 were heated under reflux for 48 hr in a flask equipped with a Dean–Stark trap and reflux condenser. No water was collected during the reaction. The solvent was then removed and the residue was dissolved in $CHCl_3$ and extracted with NH_4OH. The aqueous layer was separated and made acidic with HCl. The solid collected (2.2 g, 0.01 mol, 19%) was crystallized from Me_2CO to give pure ***N*-cyclohexyl-3,3-dimethylsuccinamic acid** (9): mp 193–194; nmr (pyridine-d_5) δ 1.52 (br, cyclohexylmethylenes), 1.55 (s, CH_3), 2.80 (s, CH_2), 4.02 (br, NCH).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.53; H, 9.42; N, 5.95.

The succinamic acid was also prepared by heating under reflux for 2 hr in C_6H_6 *gem*-dimethylsuccinic anhydride (7, 640 mg, 5 mmol) and cyclohexylamine (496 mg, 5 mmol). The solid obtained on cooling was precipitated from dilute NH_4OH with HCl to give pure 9 (1.10 g, 4.9 mmol, 98%) identical in all respects with the product from the imine condensation.

B. In Xylene.—*p*-Methoxybenzylidenecyclohexylamine (**1c**, 10.86 g, 0.05 mol) and *gem*-dimethylsuccinic anhydride (7, 6.40 g, 0.05 mol) in 50 ml of xylene were heated under reflux for 48 hr. After removal of the solvent, the oily residue was distilled at 72–135° (0.2 mm) to yield a yellow liquid (9.95 g, 58%). Glpc analysis of the distillate (5% Carbowax KOH on firebrick, 0.32 cm × 1.5 m) indicated two compounds with retention times of 4.5 min (identical with *p*-methoxybenzaldehyde) and 6.0 min. The distillate in $CHCl_3$ was stirred for 2 hr with aqueous $NaHSO_3$ (18 g in 85 ml) and, after separation, the aqueous layer was acidified with 5 ml of concentrated H_2SO_4 and then warmed on a steam bath until evolution of SO_2 ceased. The oily material which separated was extracted into $CHCl_3$, the latter was dried ($MgSO_4$), and the solvent was removed to yield *p*-methoxybenzaldehyde (1.38 g, 0.01 mol, 20%), which was identified by nmr.

The $CHCl_3$ layer obtained after the $NaHSO_3$ treatment was dried ($MgSO_4$) and the solvent was removed to yield a solid (3.02 g, 0.014 mol, 29%) mp 50–53°. Sublimation at 70° (2 mm) gave pure **1-cyclohexyl-3,3-dimethylsuccinimide** (**10**): mp 54–55°; nmr δ 1.33 (s, CH_3), 1.67 (br, cyclohexylmethylenes), 2.55 (s, O=CCH_2), 3.92 (br, NCH).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 69.13; H, 8.94; N, 6.89.

The glpc tracing of the distillate was reproduced by an equimolar mixture of *p*-methoxybenzaldehyde and **10**.

The residue from the distillation of the reaction mixture was dissolved in 5% aqueous $NaHCO_3$ and filtered, and the filtrate was acidified with concentrated HCl to pH 1 to yield a mixture of the diastereomeric acids **2g** and **3g** (4.66 g, 27%), mp 161–205°. The trans acid **2g** was obtained from the above solid by crystallization twice from Me_2CO: mp 195–196°; nmr δ 1.10 (s, CCH_3), 1.40 (s, CCH_3), 2.85 (d, $J = 9$ Hz, C-4 H), 3.77 (s, OCH_3), 4.85 (d, $J = 9$ Hz, C-5 H).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.64; H, 7.72; N, 4.02.

Treatment of this acid with EtOH–Et_2O diazomethane gave the Me ester **2g′** in 72% yield, which was crystallized from hexane for analysis: mp 115–116; nmr δ 3.58 (s, O=$COCH_3$).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.23; H, 8.13; N, 3.86.

The cis acid **3g** was obtained by crystallization of the diastereomeric mixture twice from 95% EtOH: mp 186–187°; nmr δ 1.22 (s, CCH_3), 1.25 (s, CCH_3), 3.11 (d, $J = 8$ Hz, C-4 H), 3.78 (s, OCH_3), 4.89 (d, C-5 H).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.54; H, 7.78; N, 4.11.

Treatment of this acid with EtOH–Et_2O diazomethane gave the Me ester **3g′** in 91% yield, which was crystallized from hexane for analysis: mp 97–98°; nmr δ 3.34 (s, O=$COCH_3$).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.49; H, 7.70; N, 3.86.

Registry No.—**1b**, 31235-64-0; **2b**, 31281-10-4; **2c**, 31235-65-1; **2d**, 31235-66-2; **2e**, 31235-67-3; **2g**, 31235-68-4; **2g′**, 31235-69-5; **3b′**, 31235-70-8; **3c′**, 31235-71-9; **3d**, 31235-72-0; **3e**, 31235-73-1; **3g**, 31281-11-5; **3g′**, 31235-74-2; **9**, 31235-75-3; **10**, 31235-76-4.

(7) All reactions were performed under a nitrogen atmosphere and solvents were concentrated on a rotary evaporator under vacuum. Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Except where noted, nmr spectra were recorded in the Model A-60A Varian Associates spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard (TMS = 0.0 ppm). Glpc analyses were performed on a Varian Model 90-P. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

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Esterification Kinetics of 5-Hydroxy-1,3-dioxane Derivatives with Acid Anhydrides and Acid Chlorides in Pyridine

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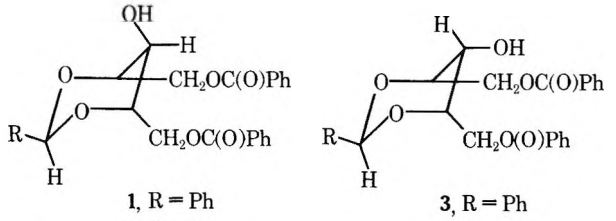
Second-order rate constants were determined for the esterification of 1,5-di-*O*-benzoyl-2,4-*O*-benzylidenexylitol (**1**) and -ribitol (**3**) and 1,5-di-*O*-benzoyl-2,4-*O*-methylenexylitol (**2**) and -ribitol (**4**) with acid anhydrides, carboxylic acid chlorides, and sulfonic acid chlorides in anhydrous pyridine. Acid anhydrides react more rapidly with compounds **3** and **4** with equatorial hydroxyl than compounds **1** and **2** with axial hydroxyl. The opposite order of reactivity was found for carboxylic acid chlorides and sulfonic acid chlorides. The Hammett correlation using σ^+ substituent constants was found to apply for reactions utilizing para-substituted benzoyl chlorides and benzenesulfonyl chlorides. Polar interactions are proposed to rationalize differences in reactivity.

Considerable attention has been directed toward comparisons of reactivities of secondary hydroxyl groups in carbohydrate derivatives in esterification and oxidation reactions.[1] Essentially all of the studies are based upon yield data and are directed toward synthetic goals rather than toward rationalization of the differences observed. Only a few esterification rate studies of alcohols with acid anhydrides or chlorides in anhydrous pyridine are reported in the literature.[2]

Four alcohols, 1,5-di-*O*-benzoyl-2,4-*O*-benzylidenexylitol (**1**) and -ribitol (**3**) and 1,5-di-*O*-benzoyl-2,4-*O*-methylenexylitol (**2**) and -ribitol (**4**), were selected as substrates for kinetic studies. These two pairs of stereoisomers had previously been found to exhibit markedly different reactivities. Hudson and coworkers[3]



1, R = Ph
2, R = H

3, R = Ph
4, R = H

reported that compound **1** was the sole isolable product in several attempts to prepare 1,3,5-tri-*O*-benzoyl-2,4-*O*-benzylidenexylitol from 2,4-*O*-benzylidenexylitol in pyridine with excess benzoyl chloride, whereas 2,4-*O*-methylenexylitol, 2,4-*O*-benzylideneribitol, and 2,4-*O*-methyleneribitol readily yield tribenzoates. Sera[4] reported that compounds **2**, **3**, and **4** are oxidized to the corresponding 3-ketoses with chromium trioxide–glacial acetic acid, but compound **1** is inert.

Amounts of compounds **1**, **2**, **3**, and **4** conveniently available for kinetic studies suggested the need for a method utilizing modest quantities. Details of the procedures developed are given in the Experimental Section. Previous studies[5] have shown that the second-order plots for reaction of alcohols and acid chlorides in pyridine are not linear. Correction for loss of acylating agent, as a consequence of hydrolysis by moisture present in pyridine, provided clean second-order plots.

Second-order rate constants are given in Table I for the esterification of compounds **1**–**4** with carboxylic acid anhydrides and acid chlorides and sulfonic acid chlorides. In comparing data obtained for reactions with acid anhydrides, several relationships emerge. The ribitol compounds (**3** and **4**) with an equatorial hydroxyl group are more reactive than the xylitol compounds (**1** and **2**), which have an axial hydroxyl group. This difference is expected on conformational grounds[6] and is the same order observed for the esterification of *cis*- and *trans*-4-phenylcyclohexanols[2a] and for *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxanes[2d] with aliphatic acid anhydrides in pyridine. The reactivity of all four substrates is substantially depressed as the number of methyl substituents on the α carbon of the anhydrides is increased. All four compounds failed to react with pivalic anhydride to an observable extent. The starting alcohols were recovered after being heated at 95° for 7 days with a 6–7-fold excess of pivalic anhydride in pyridine. The ratio of $k_{(MeCO)_2O}/k_{(EtCO)_2O}$ or $k_{(MeCO)_2O}/k_{(i\text{-}PrCO)_2O}$ is much larger for compounds **1**–**4** than for cyclohexanol and some of its derivatives. Data are given in Table II. Since the electronic effects of methyl substituents on the α carbon of the anhydrides should be similar in both series, the retarding effect observed with compounds **1**–**4** would appear to be largely steric in nature, the effect being more pronounced in the xylitol compounds **1** and **2**, in which the hydroxyl group is in the axial position.

It was somewhat surprising to observe that the rates of esterification of **1** and **3** with acetic anhydride in pyridine are greater than those of *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxanes (6×10^{-5} and 5×10^{-4} l. mol^{-1} sec^{-1}, respectively, at 25°), reported by Buck and coworkers.[2d] The presence of the bulky groups, benzoyloxymethyl, on the carbon atoms adjacent to the hydroxyl group in **1** and **3**, as contrasted to hydrogens in the other pair, might be expected to provide an inhibiting effect. Rate enhancement may be a consequence of suppression to change in ring conformation by the bulky substituents.

The greater reactivity of acid chlorides over acid anhydrides is to be expected. The greater reactivity of compounds **1** and **3**, containing the benzylidene acetal

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TABLE I
SECOND-ORDER ESTERIFICATION RATES IN PYRIDINE

Acylating agent[b]	Registry no.	T, °C	k_2[a] × 10^3 l. mol^{-1} sec^{-1} 1	2	3	4
$(MeCO)_2O$	108-24-7	25	0.335	0.146	1.62	1.26
$(MeCO)_2O$		35	0.571		2.36	
$(MeCO)_2O$		42.6	0.766		3.55	
$(MeCO)_2O$		50	1.11	0.501	4.81	3.48
$(EtCO)_2O$	123-62-6	50	0.243	0.101	1.35	1.15
$(i\text{-}PrCO)_2O$	97-72-3	50	0.0409	0.0187	0.299	0.223
i-PrCOCl	79-30-1	25	183		22.1	
PhCOCl	98-88-4	25	16.6	13.6	2.46	1.94
p-$CH_3OC_6H_4COCl$	100-07-2	25	3.18		0.547	
p-$CH_3C_6H_4COCl$	874-60-2	25	8.74		1.32	
p-FC_6H_4COCl	403-43-0	25	14.4		2.09	
p-ClC_6H_4COCl	122-01-0	25	22.2		3.07	
p-BrC_6H_4COCl	586-75-4	25	25.3		3.18	
p-$O_2NC_6H_4COCl$	122-04-3	25	162		15.7	
$MeSO_2Cl$	124-63-0	25	38.8	37.1	9.08	7.81
$MeSO_2Cl$		30			12.7	
$MeSO_2Cl$		35			16.5	
$EtSO_2Cl$	594-44-5	25	6.08	4.55	3.38	2.63
$PrSO_2Cl$	10147-36-1	25	3.16	3.00	2.54	2.41
$BuSO_2Cl$	2386-60-9	25	3.25	3.17	2.45	2.82
$PhSO_2Cl$	98-09-9	25	1.56	1.51		
p-$CH_3C_6H_4SO_2Cl$	98-59-9	25	0.75	0.90		
p-$CH_3C_6H_4SO_2Cl$		35	0.80			
p-$CH_3C_6H_4SO_2Cl$		45	1.45			
p-$CH_3OC_6H_4SO_2Cl$	98-68-0	25	0.39			
p-$FC_6H_4SO_2Cl$	349-88-2	25	1.42			
p-$ClC_6H_4SO_2Cl$	98-60-2	25	2.12			
p-$BrC_6H_4SO_2Cl$	98-58-8	25	2.53			
p-$O_2NC_6H_4SO_2Cl$	98-74-8	25	7.03			

[a] Rate constants reported are, with but few exceptions, averages of two or three duplicate runs. Deviation from the average was about ±2.5%; in many instances much less. Standard deviations of data points in establishing the best straight line within a given run were in some cases ±3% but generally much less. [b] Rates of reaction of **1** and **3** with benzoic anhydride were found to be slow and precluded determination of rate constants. However, **3** was more reactive than **1**. The same observation was made with pivaloyl chloride but the order of reactivity was **1** over **3**.

TABLE II
RATIO OF ESTERIFICATION RATE CONSTANTS

Substrate	$k_{(MeCO)_2O}/k_{(EtCO)_2O}$	$k_{(MeCO)_2O}/k_{(i\text{-}PrCO)_2O}$
1	4.6	27.1
2	5.0	26.8
3	3.6	16.1
4	3.0	15.6
Cyclohexanol[a]	1.5	1.9
cis-4-*tert*-Butylcyclohexanol[a]	1.3	1.3
trans-4-*tert*-Butyleyclohexanol[a]	1.5	2.0
trans-4-*tert*-Phenylcyclohexanol[a]		1.9

[a] Rate constants given in ref 2a.

ring, is consistent with the data obtained in esterification with acid anhydrides. The differences are smaller as would be expected because of the greater reactivity and lesser selectivity of acid chlorides. These observations suggest that the hydroxyl groups are located in much the same environment in each of the two series. Moreover, conformational changes occurring in the 1,3-dioxane rings during the course of the reactions must be limited. The difference in electronic or steric effects of phenyl *vs.* hydrogen would be expected to be small because of the distances from the reaction center. Though methanesulfonyl chloride exhibited greater reactivity toward all four alcohols than ethanesulfonyl chloride, 1-propanesulfonyl chloride, and 1-butanesulfonyl chloride, differences among the latter three were small.

The greater reactivity of acid chlorides toward the xylitol compounds with axial hydroxyl (**1** and **2**) over the ribitol compounds with equatorial hydroxyl (**3** and **4**) was unexpected, since the opposite order was observed for the carboxylic acid anhydrides. Though rate constants were not obtained using benzoic anhydride because of its relative inertness, preference of **3** and **1** was clearly established. Accordingly, relative reactivities in this sense are the same whether an aliphatic or aromatic anhydride is used as the acylating agent. However, this type of reversal in reactivities of anhydrides and acid chlorides is not without precedent in the literature.[2d] Reaction of acetic anhydride in pyridine with equimolar amounts of *cis*- (axial hydroxyl) and *trans*-5-hydroxy-2-phenyl-1,3-dioxane (equatorial hydroxyl) gave products in which the ratio of cis ester to trans ester was 1:5.8. The parallel reaction using *p*-phenylazobenzoyl chloride in pyridine provided a cis to trans product ratio of 5.6:1. A similar study with *cis*- and *trans*-4-phenylcyclohexanol demonstrated that the cis isomer (equatorial hydroxyl) was the more reactive toward both acetic anhydride and *p*-phenylazobenzoyl chloride. These and our observations suggest that the 1,3-dioxane ring has an important function in controlling reactivity. A similar comparison in the aromatic sulfonyl chloride series was not conveniently feasible since reactivities of substrates **3** and **4** were reduced to a point that kinetic measurements near ambient temperatures were precluded.

Rate constants (Table I) for reactions of para-substituted benzoyl chlorides and compounds **1** and **3** as well as para-substituted benzenesulfonyl chlorides and **1** were processed to establish Hammett correlations. Plots using σ values[7] were found to be nonlinear. Plots of log k *vs.* σ^+[8] are shown in Figure 1. Positive ρ values clearly evolve from the plots. Generally reactions giving $\rho\sigma^+$ relationships exhibit negative ρ values, for example, cumyl chloride solvolysis[8] and pyrolysis of 1-arylethyl acetates.[9] Two contrary examples[10] lending support to observations made in this study show positive ρ values in $\rho\sigma^+$ plots. In both instances, explanations are provided suggesting that the high contribution of conjugation of the substituent with the reaction site decreases in going from substrate to the activated complex in the rate-limiting process. Our data allow for a similar interpretation on the basis that substituted benzoyl chlorides interact with pyridine to form aroylpyridinium chlorides with considerable carbonium ion character.

An interpretation[2d] for the greater reactivity of *trans*-5-hydroxy-2-phenyl-1,3-dioxane toward acetic anhydride in pyridine and the cis isomer toward *p*-phenylazobenzoyl chloride in pyridine was given, based upon intramolecular hydrogen bonding. The same interpretation[2d] was provided for the observation[11] that 1,4:3,6-dianhydro-D-glucitol yields more of the 2(exo) acetate than 5(endo) acetate with acetic anhydride in pyridine but more of the 5 product when reacted with *p*-phenylazobenzoyl chloride or *p*-toluenesulfonyl chloride in pyridine. It would seem unlikely that intramolecular hydrogen bonding would persist to any extent in a pyridine solution of these compounds. Intermolecular hydrogen bonding between pyridine and alcohols is evident even in dilute solutions.[12]

Dipolar interactions greatly influence conformation of heterocyclic compounds.[13] We propose that dipolar interactions, both dipole–dipole and ion–dipole, serve as a more logical source of control of reactivity rather than hydrogen bonding effects. Acid anhydrides and acid chlorides react with pyridine to form intermediate acylpyridinium ions. The extent of conversion of acid chlorides to an acylpyridinium may be nearly quantitative.[14] On the other hand, acid anhydrides and pyridine do not yield isolable salts. The equilibration of acetic anhydride and pyridine with acetylpyridinium acetate was recently reported.[15] Thus the reactive species in acylation with an acid chloride in pyridine may be considered to be an acylpyridinium ion (**5** or **6**) while that with an acid anhydride is an ion pair (**7**). Though compounds with equatorial hydroxyl are more reactive toward acylation,[6] we suggest that the electronegative atoms in the 1,3-dioxane ring promote reactivity in the series with axial hydroxyl by interaction with the positive pyridine nitrogen. This type of interaction is precluded with the ribitol series in which hydroxyl is disposed in the equatorial position. The lack of definitive cationic character for species **7** formed from acid anhydrides and pyridine allows the normal order[6] of reactivity to prevail. The observation of positive ρ values in the Hammett $\rho\sigma^+$ correlations accords with the formation of a transition state in which the high contribution of conjugation of the substituent with the reaction site decreases. The contribution of para substituents in R_2 for structure **8** might be expected to be less than that of the same substituents in R of **5** or **6**.

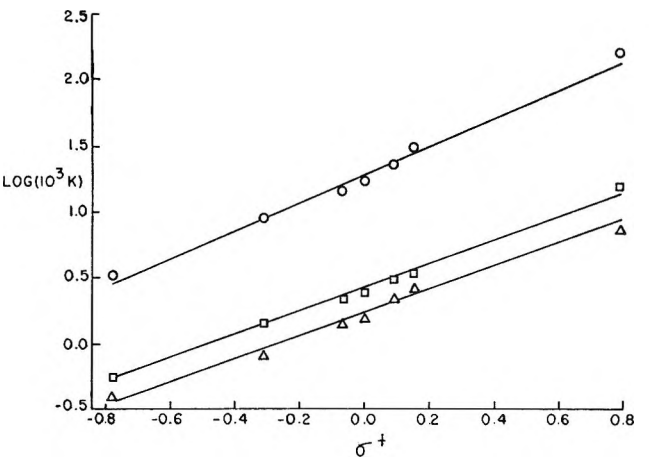
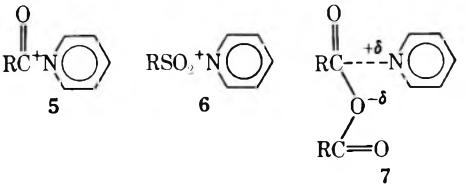
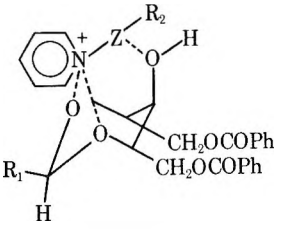


Figure 1.—Correlation of log k_2 with ρ^+. ○, **1** and para-substituted benzoyl chlorides, ρ = 0.95; linear correlation coefficient = 0.983. □, **3** and para-substituted benzoyl chlorides, ρ = 0.83; linear correlation coefficient = 0.987. △, **1** and para-substituted benzenesulfonyl chlorides, ρ = 0.85; linear correlation coefficient = 0.985.





8, Z = CO or SO_2

It is of interest to note that the contrasting reactivity of the *exo*- and *endo*-hydroxyl groups in 1,4:3,6-dianhydro-D-glucitol toward acetic anhydride and acid chlorides may be rationalized by this same interpretation. Numerous other examples may be cited and similarly interpreted; for example, the C_3-hydroxyl is more reactive than that on C_2 in methyl 4,6-*O*-benzylidene-α-D-galactopyranoside toward benzoyl chloride in pyridine, but the C_2-hydroxyl is the more reactive secondary hydroxyl in methyl 4,6-*O*-benzylidene-α-D-glycopyranoside.[16] Similarly, a variety of examples of relative reactivities of hydroxyl groups in sulfonation may be

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(11) (a) R. U. Lemieux and A. G. McInnes, *Can. J. Chem.*, **38**, 136 (1960); (b) K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *J. Chem. Soc.*, 4171 (1963).
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rationalized by this interpretation. Some are the greater reactivity of the 5-hydroxyl over the 2-hydroxyl in 1,4:3,6-dianhydro-D-glucitol toward *p*-toluenesulfonyl chloride;[11a] the greater reactivity of 1,4:3,6-dianhydro-D-glucitol 2-*p*-toluenesulfonate over 1,4:3,6-dianhydro-D-glucitol 5-*p*-toluenesulfonate toward *p*-toluenesulfonyl chloride;[11b] and preference for 3-O-tosylation in methyl 4,6-*O*-benzylidene-α- (or -β-) D-galactopyranoside.[17] Numerous other examples described[18] may be similarly rationalized.

Rate measurements at several temperatures were determined for a few of the reactions studies. Data are given in Table I. Activation parameters calculated are listed in Table III. This limited study of temperature dependence precludes generalization.

TABLE III

ACTIVATION PARAMETERS[a]

Reactions	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S_{25}^{\ddagger}$, eu
1 + $(MeCO)_2O$	8.4 ± 0.3	−46 ± 4
2 + $(MeCO)_2O$	8.8	−47
3 + $(MeCO)_2O$	7.7 ± 0.2	−45 ± 4
4 + $(MeCO)_2O$	7.1	−48
1 + p-$CH_3C_6H_4SO_2Cl$	11.0 ± 0.7	−51 ± 4
3 + CH_3SO_2Cl	12.2 ± 0.4	−26 ± 9

[a] Standard deviations given.

Experimental Section[19]

Pyridine was refluxed over BaO for 16–24 hr and then fractionally distilled through a packed column. The fraction boiling at 114–114.5° was collected in a moisture-protected receiver and stored over KOH pellets in an automatic buret. Aniline, used for determining per cent anhydride, was distilled prior to use, collecting that fraction boiling at 88° (21–22 mm). All acylating agents were purified by distillation and/or recrystallization: acetic anhydride, bp 139° (745 mm); propionic anhydride, bp 68–69° (20 mm); isobutyric anhydride, bp 75–76° (20 mm); pivalic anhydride, bp 98–99° (31 mm); isobutyryl chloride, bp 91°; benzoyl chloride, bp 93° (21 mm); *p*-chlorobenzoyl chloride, 108–109° (12 mm); *p*-fluorobenzoyl chloride, bp 81° (12 mm); *p*-anisoyl chloride, bp 141° (12 mm); *p*-toluoyl chloride, bp 102° (15 mm); *p*-bromobenzoyl chloride, mp 38–39° (recrystallized from dry, low-boiling ligroin); *p*-nitrobenzoyl chloride, mp 71–72° (recrystallized from dry, low-boiling ligroin); methanesulfonyl chloride, bp 57–58° (12 mm); ethanesulfonyl chloride, bp 73° (18 mm); 1-propanesulfonyl chloride, bp 81–85° (15 mm); 1-butanesulfonyl chloride, bp 98–101° (18 mm); benzenesulfonyl chloride, bp 92° (16 mm); *p*-toluenesulfonyl chloride, bp 87–88° (14 mm); *p*-chlorobenzenesulfonyl chloride, bp 97–100° (15 mm), mp 50° (recrystallized from chloroform–ligroine); *p*-bromobenzenesulfonyl chloride, bp 141–142° (5 mm), mp 68° (recrystallized from ligroin); *p*-fluorobenzenesulfonyl chloride, mp 32° (recrystallized from ligroin); *p*-nitrobenzenesulfonyl chloride, mp 80° (recrystallized from ligroin); and *p*-methoxybenzenesulfonyl chloride, mp 42° (recrystallized from chloroform–ligroin).

1,5-Di-*O*-benzoyl-2,4-*O*-benzylidenexylitol (1) was prepared by the method of Hann, Ness, and Hudson[3] with some modifications. The filtrate containing the cleavage product from the reaction of 2,4-*O*-benzylidene-D-glucitol and sodium metaperiodate was cooled and $NaBH_4$ (20% excess) was slowly added. After 30 hr at room temperature, the pH of the reaction mixture was adjusted to approximately 5 by addition of 3 *M* acetic acid and filtered, and resulting solution was concentrated on an air stream. The recrystallized product melted at 149.5–150° (reported[3] mp 148–149°).

1,5-Di-*O*-benzoyl-2,4-*O*-methylenexylitol (2) was prepared by modification of the method of Hann, Ness, and Hudson.[20] $NaBH_4$ (20% excess) was slowly added to the ice–water-cooled filtrate containing the cleavage product from the reaction of 2,4-*O*-methylene-D-glucitol (10.0 g) and sodium metaperiodate. The solution was allowed to stand at room temperature for 30 hr and then an ion exchanger (H^+ form) was added to the reaction mixture and after 30 min the solution was filtered and the filtrate air-evaporated. The resulting residue was dissolved in 100 ml of CH_3OH and vacuum evaporated. This was repeated twice. Extraction of the residue for 48 hr by means of a Soxhlet extractor using 300 ml of $CHCl_3$ provided impure 2,4-*O*-methylenexylitol upon evaporation of solvent. Following two recrystallizations from absolute EtOH, benzoylation was effected using 2.2 mol of acylating agent per mol of the 2,4-*O*-methylenexylitol to provide product, mp 140–141° (reported[20] mp 139–140°).

1,5-Di-*O*-benzoyl-2,4,*O*-benzylideneribitol, mp 136.5–138°, was prepared by the method previously reported.[21]

1,5-Di-*O*-benzoyl-2,4,*O*-methyleneribitol, mp 164–166°, was prepared by the method previously reported.[22]

3-*O*-Acyl Derivatives of Compounds 1–4.—To a cold solution of 0.2–0.3 g of alcohol in 10 ml of anhydrous pyridine, 2–3-mol excess of the acylating or sulfonating agent was added dropwise. After the solution was allowed to stand at room temperature for 24–48 hr, a few drops of H_2O was added, and then the mixture was poured into 300–400 ml of 10–15% aqueous $NaHCO_3$. The aqueous solution was extracted with $CHCl_3$ and the extract washed successively with 1 *N* HCl, 5% aqueous $NaHCO_3$, and H_2O. The chloroform solution was dried over anhydrous $CaCl_2$, filtered, and evaporated to dryness. The crude products, obtained in essentially quantitative yield, were recrystallized 4–5 times from EtOH and dried *in vacuo*. Analytical data are given in Table IV.

Kinetic Method.—The typical method[2a] of following esterification kinetics by volumetric titration was modified by utilizing an automatic titration procedure requiring less than 0.2 g of alcohol, **1–4**, per kinetic run. The automatic titrator consisted of a Radiometer TTT 11 control unit and a titration assembly designed by Stewart[23] with a sensitivity of 5×10^{-5} ml.

Preliminary experiments demonstrated that excess anhydride in pyridine is almost instantaneously hydrolyzed upon addition of small amounts of H_2O to yield 2 mol of acid in the quenching process. Hydrolysis of ester under conditions imposed was not detectable. Thus the decrease in acid titer as the reaction proceeds is directly related to the amount of ester formed or to the amount of alcohol and anhydride consumed.

In a typical kinetic run, the alcohol (about 4×10^{-4} mol), **1–4**, was accurately weighed into a 10-ml volumetric flask and dissolved by partially filling the flask with anhydrous pyridine. A 10-ml stock solution of the anhydride in pyridine was prepared so that the number of moles of anhydride[24] in a 1-ml aliquot of the stock solution equaled the number of moles of alcohol weighed out. Then 1 ml of the stock solution was added to the alcohol solution and anhydrous pyridine added to provide 10 ml of reaction mixture. The flask was sealed with a serum cap and placed in a constant temperature bath (±0.1°). Aliquots of 1 ml were withdrawn periodically with a syringe, previously purged with dry N_2 to minimize introduction of moisture into the reaction mixture. Each aliquot was quenched by introduction into a 100-ml beaker containing a few drops of H_2O, and the resulting solution was stirred for 1–2 min. An additional 10 ml of H_2O was added and the mixture stirred until the alcohol and ester precipitated or oiled out. CCl_4 (10 ml) was added to the beaker to dissolve the alcohol and ester and to depress the extent of hydrolysis of the ester during the titration. Another 30 ml of H_2O was added and the resulting mixture was titrated to a pH of 8.7 with standard NaOH, contained in the 1-ml titrator syringe.

The kinetic method was modified in one respect for acid chlorides. An infinite-time titrimetric method[2b] was employed in order to make a correction for water contained in the pyridine. Although good linear plots up to 60–75% conversion were ob-

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(23) We thank Dr. J. Stewart, University of North Dakota, Grand Forks, for allowing us to fabricate a unit, following his design.

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TABLE IV

3-*O*-ACYL AND SULFONYL DERIVATIVES OF COMPOUNDS 1–4

Compd[a]	Mp, °C	Compd[a]	Mp, °C
3-*O*-Acetyl-1	128.5–129[b]	1 3-benzenesulfonate	153–154
3-*O*-Propionyl-1	99–100	1 3-*p*-toluenesulfonate	156–157
3-*O*-Isobutyryl-1	96.5–97.5	1 3-*p*-nitrobenzenesulfonate	158–159
3-*O*-Acetyl-2	176.5–177[c]	1 3-*p*-bromobenzenesulfonate	161–163
3-*O*-Propionyl-2	104–105	1 3-*p*-chlorobenzenesulfonate	160–162
3-*O*-Isobutyryl-2	79–80	1 3-*p*-fluorobenzenesulfonate	167–168
3-*O*-Acetyl-3	108–109[d]	1 3-*p*-methoxybenzenesulfonate	162–163
3-*O*-Propionyl-3	121–122	1 3-methanesulfonate	178–179
3-*O*-Isobutyryl-3	101.5–102	1 3-ethanesulfonate	180–182
3-*O*-Acetyl-4	101.5–102.5	1 3-(1-propanesulfonate)	181–182
3-*O*-Propionyl-4	100–100.5	1 3-(1-butanesulfonate)	182–184
3-*O*-Isobutyryl-4	55–57	2 3-benzenesulfonate	143–144
3-*O*-Benzoyl-1	128–129	2 3-*p*-toluenesulfonate	146–147
3-*O*-*p*-Bromobenzoyl-1	120–121	2 3-methanesulfonate	166–168
3-*O*-*p*-Chlorobenzoyl-1	108–109	2 3-ethanesulfonate	167–169
3-*O*-*p*-Fluorobenzoyl-1	103–104.5	2 3-(1-propanesulfonate)	168–169
3-*O*-*p*-Anisoyl-1	97–98.5	2 3-(1-butanesulfonate)	169–170
		3 3-methanesulfonate	135–137
3-*O*-*p*-Toluoyl-1	116–117	3 3-ethanesulfonate	136–138
3-*O*-*p*-Nitrobenzoyl-1	142.5–144	3 3-(1-propanesulfonate)	137–138
3-*O*-Benzoyl-2	118–119[e]	3 3-(1-butanesulfonate)	138–140
3-*O*-Benzoyl-3	129–130[f]	4 3-methanesulfonate	180–182
3-*O*-*p*-Bromobenzoyl-3	158–159	4 3-ethanesulfonate	182–183
3-*O*-*p*-Chlorobenzoyl-3	147–148	4 3-(1-propanesulfonate)	183–184
3-*O*-*p*-Fluorobenzoyl-3	135.5–136.5	4 3-(1-butanesulfonate)	184–186
3-*O*-*p*-Anisoyl-3	106–107		
3-*O*-*p*-Toluoyl-3	101–102		
3-*O*-*p*-nitrobenzoyl-3	138–139		
3-*O*-*p*-Benzoyl-4	110.5–111[g]		

[a] Satisfactory combustion analytical data (±0.4%) were provided for all new compounds: Ed. [b] Reported mp 128–129°: G. Y. Wu and J. M. Sugihara, *Carbohyd. Res.*, **13**, 89 (1970). [c] Reported mp 174.5–175°, ref 4. [d] Reported mp 108–109°, reference in *b*. [e] Reported mp 117–118°, ref 20. [f] Reported mp 108–109, ref 21. [g] Reported mp 109–110°, ref 22.

tained for the acid anhydrides, curvature early in the kinetic run was observed for reactions with acid chlorides. The curvature is attributable to traces of water in the pyridine. Since the rate of hydrolysis of acid chlorides is considerably greater than the rate of esterification, the actual concentration of acid chloride was considered to be equal to the initial concentration minus the amount hydrolyzed.

Slopes for second-order rate plots were determined by the method of least squares[25] and processed on a computer. Activation parameters were calculated by applying the absolute rate equation.[26] For kinetic runs carried out at temperatures above 25°, corrections were made to account for thermal expansion of pyridine.

Registry No.—**1**, 31568-92-0; 3-*O*-propionyl-**1**, 31568-93-1; 3-*O*-isobutyryl-**1**, 31568-94-2; 3-*O*-benzoyl-**1**, 31568-95-3; 3-*O*-*p*-bromobenzoyl-**1**, 31568-96-4; 3-*O*-*p*-chlorobenzoyl-**1**, 31615-31-3; 3-*O*-*p*-fluorobenzoyl-**1**, 31568-97-5; 3-*O*-*p*-anisoyl-**1**, 31568-98-6; 3-*O*-*p*-toluoyl-1, 31568-99-7; 3-*O*-*p*-nitrobenzoyl-**1**, 31569-00-3; **1** 3-benzenesulfonate, 31569-01-4; **1** 3-*p*-toluenesulfonate, 31569-02-5; **1** 3-*p*-nitrobenzenesulfonate, 31569-03-6; **1** 3-*p*-bromobenzenesulfonate, 31569-04-7; **1** 3-*p*-chlorobenzenesulfonate, 31569-05-8; **1** 3-*p*-fluorobenzenesulfonate, 31569-06-9; **1** 3-*p*-methoxybenzenesulfonate, 31569-07-0; **1** 3-methanesulfonate, 31569-08-1; **1** 3-ethanesulfonate, 31569-09-2; **1** 3-(1-propanesulfonate), 31569-10-5; **1** 3-(1-butanesulfonate), 31569-11-6; **2**, 31569-12-7; 3-*O*-propionyl-**2**, 31569-13-8; 3-*O*-isobutyryl-2, 31569-14-9; **2** 3-benzenesulfonate, 31569-15-0; **2** 3-*p*-toluenesulfonate, 31569-16-1; **2** 3-methanesulfonate, 31569-17-2; **2** 3-ethanesulfonate, 31569-18-3; **2** 3-(1-propanesulfonate), 31569-19-4; **2** 3-(1-butanesulfonate), 31569-20-7; **3**, 31569-21-8; 3-*O*-propionyl-**3**, 31569-22-9; 3-*O*-isobutyryl-**3**, 31569-23-0; 3-*O*-*p*-bromobenzoyl-**3**, 31569-24-1; 3-*O*-*p*-chlorobenzoyl-**3**, 31569-25-2; 3-*O*-*p*-fluorobenzoyl-**3**, 31569-26-3; 3-*O*-*p*-anisoyl-**3**, 31569-27-4; 3-*O*-*p*-toluoyl-**3**, 31569-28-5; 3-*O*-*p*-nitrobenzoyl-**3**, 31569-29-6; **3** 3-methanesulfonate, 31569-30-9; **3** 3-ethanesulfonate, 31569-31-0; **3** 3-(1-propanesulfonate), 31638-55-8; **3** 3-(1-butanesulfonate), 31569-32-1; **4**, 31569-33-2; 3-*O*-acetyl-**4**, 31569-34-3; 3-*O*-propionyl-**4**, 31569-35-4; 3-*O*-isobutyryl-**4**, 31569-36-5; **4** 3-methanesulfonate, 31569-37-6; **4** 3-ethanesulfonate, 31569-38-7; **4** 3-(1-propanesulfonate), 31569-39-8; **4** 3-(1-butanesulfonate), 31572-15-3.

Acknowledgment.—The support by the National Science Foundation (GP-5736) is gratefully acknowledged.

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Kinetics and Mechanism for Benzaldehyde Phenylhydrazone Formation[1]

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Benzaldehyde phenylhydrazone formation, like semicarbazone, thiosemicarbazone, oxime, and Schiff base formation, occurs with rate-determining attack of the nucleophilic reagent under slightly acidic conditions and with rate-determining dehydration of the carbinolamine intermediate under neutral and basic conditions. The attack of phenylhydrazine on *p*-chloro-, unsubstituted, *p*-methoxy-, and *p*-hydroxybenzaldehyde is subject to general acid catalysis by carboxylic acids and the conjugate acid of the nucleophile while that on *p*-nitrobenzaldehyde is subject to catalysis by carboxylic acids and apparent inhibition by carboxylate ions. Rate constants for the hydrated proton, chloroacetic acid, acetic acid, phenylhydrazinium ion, and water as catalysts for the attack of phenylhydrazine on a series of substituted benzaldehydes are well correlated by the σ^+ substituent constants. The derived values of ρ^+ increase linearly with increasing pK_a of the catalyst. The dehydration of the carbinolamines derived from phenylhydrazine and benzaldehydes exhibits both acid-catalyzed and pH-independent reactions and, in the case of that derived from *p*-nitrobenzaldehyde, a base-catalyzed reaction as well.

The addition of amines to carbonyl compounds has been the subject of a number of studies in recent years. Two excellent reviews of this topic have appeared.[3,4]

It has been established that the formation of oximes,[5] semicarbazones,[5,6] thiosemicarbazones,[7] phenylhydrazones,[8] and Schiff bases[9-12] occurs with rate-determining attack of the nucleophilic reagent under slightly acidic conditions. This step is generally subject to both general acid and specific acid catalysis for the cases of weakly basic amines but is insensitive to such catalysis when the nucleophile is strongly basic.[3,4] Under neutral or basic conditions, dehydration of the carbinolamine becomes the rate-determining step. This

$$\text{C=O} + \text{RNH}_2 \rightleftharpoons \text{—CNHR (OH)} \rightleftharpoons \text{C=NR} + \text{H}_2\text{O} \quad (1)$$

step is generally subject to strong acid catalysis although pH-independent and base-catalyzed processes also occur in some cases (eq 1).[3,4,7]

In this work, a previous study[8] of benzaldehyde phenylhydrazone formation has been elaborated to include a series of substituted benzaldehydes. Attention is focused on the susceptibility of the various steps to acid catalysis and on the influence of substituents on the pertinent rate constants. While the results are generally consistent with those observed previously in a parallel study of semicarbazone formation,[6] several differences were found. Details are presented herein.

Experimental Section

Materials.—All reagents employed were obtained commercially and, with the exception of reagent grade inorganic salts, were either redistilled or recrystallized before use. Solutions of phenylhydrazine were prepared just prior to use. Solutions of carboxylic acids in 20% ethanol were prepared just prior to use to avoid esterification.

Kinetic measurements were carried out spectrophotometrically at 25° with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder. The reaction of benzaldehyde and phenylhydrazine was followed by observing the appearance of the product at 340 nm (*p*-hydroxybenzaldehyde at 330, *p*-methoxybenzaldehyde at 340, *p*-chlorobenzaldehyde at 348, and *p*-nitrobenzaldehyde at 420 nm), with an initial concentration of aldehyde of 5×10^{-5} *M*. In all cases, a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from slopes of plots of log $(OD_\infty - OD_t)$ against time in the usual manner. Second-order rate constants were obtained by dividing the first-order constants by the concentration of nucleophilic reagent in the reactive, free base form. When necessary, corrections for catalysis by the conjugate acid of the nucleophile were made as previously described.[6] Kinetic measurements were carried out in 20% ethanol at an ionic strength of 0.50, maintained with KCl, in the presence of 2×10^{-4} *M* EDTA. Values of apparent pH were recorded with a Radiometer Model PHM 4d meter.

Sayer and Jencks have pointed out that neglecting the influence of the rate of carbinolamine dehydration on rate constants measured under conditions in which amine addition is predominantly rate determining can introduce appreciable errors into rate constants for the latter process.[7] The necessary correction takes the form: $k_{addn} = k_{uncor}/(1 - k_{uncor}/k_{dehyd}\ a_{H^+})$ in which k_{addn} is the second-order rate constant for the addition reaction, k_{uncor} is the uncorrected (measured) second-order rate constant for this reaction, k_{dehyd} is the third-order rate constant for acid-catalyzed carbinolamine dehydration, and a_{H^+} is the hydrogen ion activity. It has been clearly shown that it is important to make these corrections for both thiosemicarbazone and semicarbazone formation from benzaldehydes.[7] In the present case, such a correction introduces no appreciable changes in the rate constants under consideration. Clearly, the importance of the correction depends principally upon the relative magnitudes of the third-order rate constants for acid-catalyzed carbinolamine dehydration and acid-catalyzed amine attack; the greater the ratio between these constants, the less important becomes the correction. In the case of semicarbazone formation from *p*-nitrobenzaldehyde, the ratio of these rate constants is 20;[6] in contrast, the same ratio for phenylhydrazone formation from this substrate is 150. Consequently, provided that one does not employ a pH too near that at which dehydration becomes rate-determining or too high buffer concentrations, the correction for phenylhydrazone formation from *p*-nitrobenzaldehyde is negligible. The necessary precautions have been observed and actual calculations of second-order rate constants with and without the correction usually differ by less than 3%. For the other aldehydes employed in the present study, the correction is even less important.

Results

Figure 1 exhibits the curves obtained by plotting second-order rate constants for the reaction of phenyl-

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(2) This investigtion was carried out by M. P. Bastos during the tenure of a Fellowship from the Fundacão de Amparo a Pesquisa do Estado de São Paulo.

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TABLE I

CATALYTIC CONSTANTS OF SEVERAL ACIDS FOR THE ATTACK OF PHENYLHYDRAZINE ON A SERIES OF BENZALDEHYDES IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50[a]

Benzaldehyde	H_3O^+ × 10^{-5}	CNAcOH × 10^{-4}	ClAcOH × 10^{-4}	HCO_2H × 10^{-4}	$BrCH_2AcOH$ × 10^{-3}	AcOH × 10^{-3}	PHH^+[b] × 10^{-4}	H_2O[c]
p-Nitrobenzaldehyde	30	39	32	13	90	55	7.3	7
p-Chlorobenzaldehyde	12	7.6	6.6	4.0	37	17	23	23
Benzaldehyde[d]	9.0	9.5	5.9	5.0	54	15	22	20
p-Methoxybenzaldehyde	1.6	1.7	1.0	0.47	6.5	2.2	2.3	2
p-Hydroxybenzaldehyde	1.7	1.3	0.96	0.40	3.4	1.7	1.4	1.5

[a] Catalytic constants have the units M^{-2} min^{-1}. [b] Phenylhydrazinium ion. [c] Reference 8, with exception of the value for AcOH. [d] Approximate values.

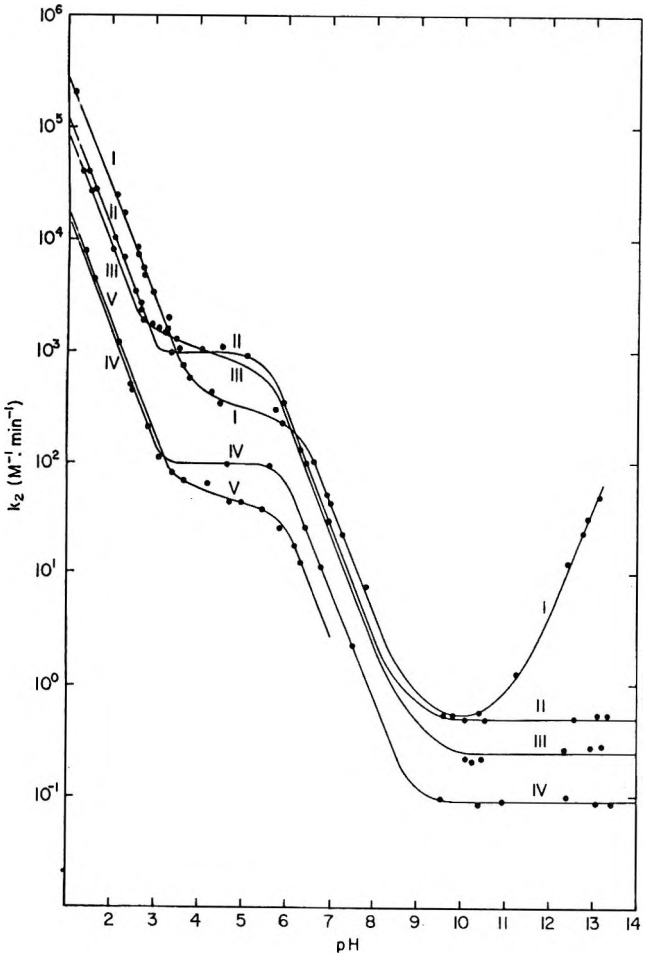


Figure 1.—Logarithms of second-order rate constants for substituted benzaldehyde phenylhydrazone formation in 20% ethanol at 25° and ionic strength 0.50 plotted as function of pH. All points are extrapolated to zero buffer concentration. Curve I, *p*-nitrobenzaldehyde; II, *p*-chlorobenzaldehyde; III, benzaldehyde; IV, *p*-methoxybenzaldehyde; and V, *p*-hydroxybenzaldehyde.

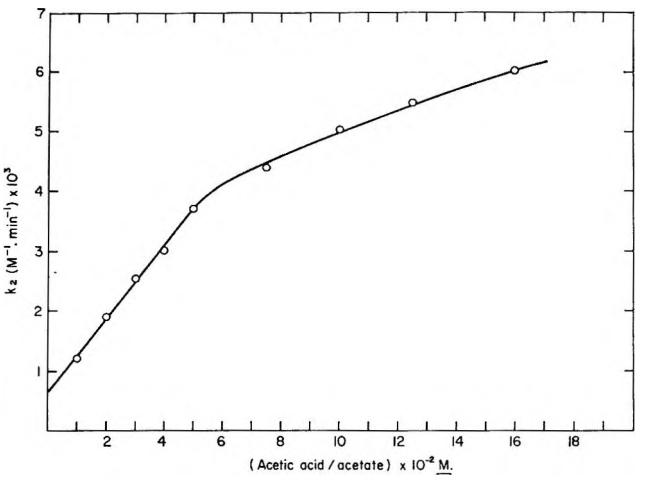


Figure 2.—Second-order rate constants for *p*-nitrobenzaldehyde phenylhydrazone formation as a function of acetic acid plus acetate buffer concentration in 20% ethanol, at 25° and ionic strength 0.50, pH 3.87.

hydrazine with various para-substituted benzaldehydes in 20% ethanol, at 25° and ionic strength 0.50, as a function of pH. Each rate constant shown was obtained by extrapolation to zero buffer concentration. The pH-rate dependence is related to that previously obtained for the formation of benzaldehyde semicarbazones[6] and thiosemicarbazones,[7] of benzaldehyde phenylhydrazone,[8] and of benzaldehyde oxime[8] and may be interpreted in the same manner.[3-9]

Under conditions more acidic than pH 6 (Figure 1), in which attack of phenylhydrazine is rate determining, second-order rate constants for phenylhydrazone formation from each of the benzaldehydes are sensitive functions of the nature and concentration of the carboxylic acid–carboxylate buffer employed to maintain constant pH. Except in one case (see below) buffers employed include cyanoacetate, chloroacetate, formate, β-bromopropionate, and acetate, each at concentrations of 0.05, 0.10, 0.15, 0.20, and 0.25 *M*.

With the exception of *p*-nitrobenzaldehyde, the buffer catalysis for phenylhydrazone formation proved straightforward; measurement of the catalytic effect as a function of the ratio of acidic and basic forms of the buffers established that the catalysis is, within experimental error, of the general acid type. That is, slopes of plots of second-order rate constants against the concentration of the acidic component of the buffer yield straight lines with equal slopes regardless of the buffer composition. Catalytic constants were obtained directly from these slopes. Such behavior is concordant with that previously observed for benzaldehyde phenylhydrazone formation in particular[8] and with reactions of this class generally.[3,4] The catalytic rate constants derived from the data in Figure 1 and from the studies or buffer catalysis are collected in Table I.

p-Nitrobenzaldehyde exhibits unique behavior in its reaction with phenylhydrazine. In the first place, plots of second-order rate constants against buffer concentration were generally nonlinear; one example, for catalysis by acetate buffers, is shown in Figure 2. Note that the plot is straight up to a concentration of about 0.10 *M* total buffer and then appears to approach a limiting rate constant with further increases in buffer concentration. Related behavior was observed for other buffer systems. As a consequence of this behavior, quantitative evaluation of buffer effects for the attack of

phenylhydrazine on *p*-nitrobenzaldehyde has been restricted to buffer concentrations of not more than 0.10 *M*.

In the second place, the behavior exhibited in Figure 2 may be accounted for in terms of inhibition of the reaction by carboxylate ions, although other explanations are in theory possible (see Discussion).

In Table II, second-order rate constants for this reaction are collected as a function of the concentration

TABLE II

VARIATION OF SECOND-ORDER RATE CONSTANTS FOR ATTACK OF PHENYLHYDRAZINE ON *p*-NITROBENZALDEHYDE IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50 AS FUNCTION OF THE CONCENTRATION OF SEVERAL CARBOXYLIC ACID–CARBOXYLATE BUFFERS[a]

Total buffer concn, *M*	% of buffer in basic form		
	Cyanoacetate Buffers		
	20, pH 2.24	50, pH 2.75	80, pH 3.23
0.020	21	7.1	2.5
0.040	24	9.2	3.2
0.060	30	11	3.9
0.080	34	13	4.6
0.10	39	15	5.3
	Chloroacetate Buffers		
	20, pH 2.62	50, pH 2.95	80, pH 3.31
0.020	11	5.0	2.9
0.040	14	6.4	3.7
0.060	17	8.3	4.4
0.080	21	10	5.1
0.10	24	12	5.8
	Formate Buffers		
	20, pH 3.17	50, pH 3.81	80, pH 4.30
0.020	4.5	0.88	0.54
0.040	5.3	1.2	0.63
0.060	6.1	1.4	0.67
0.080	6.8	1.6	0.74
0.10	7.1	1.7	0.79
	Bromopropionate Buffers		
	10, pH 3.31	20, pH 3.62	30, pH 3.84
0.010	2.2	1.3	0.95
0.020	3.0	1.9	1.4
0.030	3.6	2.5	1.9
0.040	4.3	3.0	2.3
0.050	5.0	3.6	2.7
	Acetate Buffers		
	10, pH 3.82	15, pH 4.03	20, pH 4.52
0.010	1.0	0.81	0.49
0.020	1.4	1.1	0.64
0.030	1.7	1.3	0.77
0.040	2.1		
0.050	2.5		

[a] Rate constants have the units of M^{-1} min^{-1} and have been multiplied by 10^{-3}.

of several buffers at various degrees of neutralization. Plots of these rate constants against the concentration of the acidic and basic components of these buffers yield straight lines (deviations are observed at higher buffer concentrations) whose slopes are collected in Table III. Note that neither of the slopes is constant indicating that the catalysis is neither simple general acid nor simple general base. In fact, both sets of

TABLE III

SLOPES OF PLOTS OF SECOND-ORDER RATE CONSTANTS FOR ATTACK OF PHENYLHYDRAZINE ON *p*-NITROBENZALDEHYDE IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50 AGAINST THE CONCENTRATION OF CARBOXYLIC ACID–CARBOXYLATE BUFFERS[a]

pH	% of buffer in basic form	Concn range, *M*	Slope (RCO_2H)	Slope (RCO_2^-)
		Cyanoacetate Buffers		
2.24	20	0.02–0.10	35	54
2.75	50	0.02–0.10	32	16
3.23	80	0.02–0.10	24	4.0
		Chloroacetate Buffers		
2.62	20	0.02–0.10	25	48
2.95	50	0.02–0.10	19	17
3.31	80	0.02–0.10	13	5.0
		Formate Buffers		
3.17	20	0.02–0.10	9.6	38
3.81	50	0.02–0.10	5.6	4.9
4.30	80	0.02–0.10	3.2	0.85
		β-Bromopropionate Buffers		
3.31	10	0.01–0.05	8.1	41
3.62	20	0.01–0.05	7.4	18
3.84	30	0.01–0.05	7.0	9.7
		Acetate Buffers		
3.82	10	0.01–0.05	4.1	35
4.03	15	0.01–0.05	3.2	16
4.52	20	0.01–0.05	2.2	3.9

[a] The slopes have the units of M^{-2} min^{-1} and have been multiplied by 10^{-4}.

slopes decrease with increasing fraction of the basic component of the buffer suggesting a combination of general acid catalysis and carboxylate inhibition.

For calculation of the concentration of the acidic component of the buffers, values of pK_a which refer to water have been used throughout. Since the solvent employed is 20% ethanol in water, which will have the effect of raising the pK_a value about 0.4 units,[13] it is important to ensure that the unusual results obtained with *p*-nitrobenzaldehyde do not reflect simply the choice of pK_a values. Note that the use of an ionic strength of 0.50 will diminish the pK_a values by about 0.2 units, compensating in part for the effect of the partially organic solvent. Three lines of evidence establish that the unusual behavior encountered for catalysis of the attack of phenylhydrazine on *p*-nitrobenzaldehyde is real. In the first place, this behavior is observed only with the indicated substrate; were a systematic error being introduced through use of inappropriate values of pK_a, similar behavior ought to have been observed for all of the aldehydes. In the second place, the trend toward decreasing catalytic constants with increasing fraction of base present is also observed if one employs the concentrations of the acidic species added to the solution rather than those calculated from values of pH and pK_a. Finally, choice of a value of pK_a lower than the true one has the effect of diminishing the calculated concentration of the acidic component for all values of pH but with greatest effect for the most basic solutions. This would result in increasing catalytic constants with increasing pH, just the opposite of the observed behavior. If anything, use of the indicated values of pK_a

(13) B. Gutbezahl and E. Grunwald, *J. Amer. Chem. Soc.*, **75**, 565 (1952), and references cited therein.

has tended to diminish the observed trend, not to accentuate it.

Inhibition by the carboxylate ions can be accounted for by assuming the formation of unreactive adducts between the aldehyde and these ions (eq 2). Defining

$$NB + A^- \rightleftharpoons U^- \quad (2)$$

K_e as the association constant for eq 2, the rate law for the reaction becomes

$$k_2 = \frac{k_0 + k_{HA}(HA) + k_H(H^+)}{1 + K_e(A^-)} \quad (3)$$

The data of Table III have been fitted to eq 3 by least-squares analysis employing a computer; the best values for catalytic constants for *p*-nitrobenzaldehyde have been included in Table I and the best values of K_e are collected in Table IV.

TABLE IV
APPARENT ASSOCIATION CONSTANTS FOR FORMATION OF UNREACTIVE ADDUCTS BETWEEN CARBOXYLATE IONS AND *p*-NITROBENZALDEHYDE IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50

Inhibitor	pK_b	K_e, M^{-1}
$CNAcO^-$	11.55	2.3
$ClAcO^-$	11.10	4.6
HCO_2^-	10.25	5.1
$BrCH_2AcO^-$	10.00	5.7
AcO^-	9.24	8.8

The attack of phenylhydrazine on benzaldehydes is also susceptible to catalysis by the phenylhydrazinium ion, since second-order rate constants, determined at pH 5.2, increase as a function of the phenylhydrazine concentration. Plots of the second-order rate constants against concentration of phenylhydrazinium ion has permitted determination of the values of the catalytic constants for that acid; these are included in Table I.

Correlation of the catalytic constants of carboxylic acids for substituted benzaldehyde phenylhydrazone formation in Brønsted plots by least-square analysis yields the following values for α: *p*-hydroxybenzaldehyde, 0.35; *p*-methoxybenzaldehyde, 0.36; *p*-chlorobenzaldehyde, 0.36; and *p*-nitrobenzaldehyde, 0.36. The values determined in this work for substituted benzaldehydes are significantly greater than that previously determined for benzaldehyde itself.[8]

The equilibrium constant K_e, defined by eq 2 (Table IV), for the formation of unreactive adducts between *p*-nitrobenzaldehyde and carboxylate ions, have been correlated with appropriate values of pK_b in a Brønsted plot. By least-square analysis, a value of 0.25 for β has been obtained.

In Figure 3, values of the catalytic constants for the hydrated proton, chloroacetic acid, acetic acid, phenylhydrazinium ion, and water are plotted against the σ^+ substituent constants.[14] In all cases good correlations have been obtained with the exception of the point for the catalytic constant of water for phenylhydrazine attack on *p*-nitrobenzaldehyde. The ρ^+ values are as follows: hydrated proton, 0.86; chloroacetic acid, 0.95; acetic acid, 0.98; phenylhydrazinium ion, 1.0; and water, 1.2. There is better correlation between the catalytic constants and σ^+ than σ, which reflects the high degree of stabilization of carbonyl compounds by para substituents capable of donating electrons by resonance. Related results have been obtained for benzaldehyde semicarbazone formation.[6]

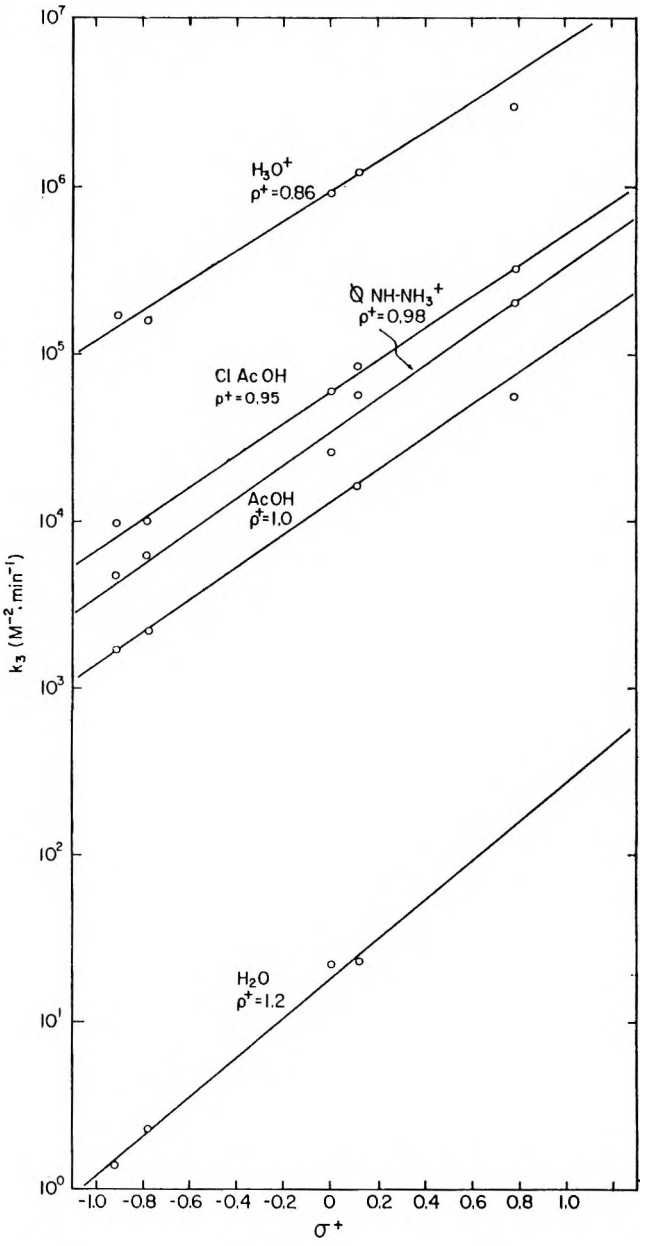


Figure 3.—Logarithms of catalytic constants for the hydrated proton, chloroacetic acid, acetic acid, phenylhydrazinium ion, and water for the attack of phenylhydrazine on a series of substituted benzaldehydes in 20% ethanol, at 25° and ionic strength 0.50, plotted against σ^+ substituent constants. The benzaldehydes employed and the numerical values of the catalytic constants are listed in Table I.

Dehydration of the intermediate carbinolamine is the rate-determining step above pH 5. It is difficult to determine spectrophotometrically the equilibrium constants for the formation of the carbinolamines from benzaldehydes and phenylhydrazine due to the strong interference absorption of the latter substance. Similar difficulties have been noted in attempts to determine the equilibrium constant for formation of the carbinolamine from ethyl pyruvate and phenylhydrazine.[5] However, with each of the benzaldehydes, the reaction is first-order in phenylhydrazine concentration over the concentration range of 5.0×10^{-3} to 5.0×10^{-2} *M*.

(14) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1959).

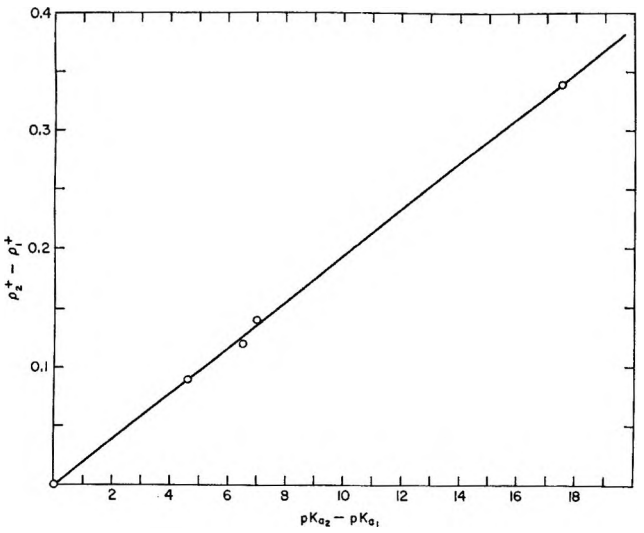


Figure 4.—Variation of ρ^+ values for the catalytic constants of several acids for the attack of phenylhydrazine on para-substituted benzaldehydes, in 20% ethanol at 25° and ionic strength 0.50, as a function of the pK_a of the catalysts.

Consequently, all kinetic studies above pH 5 have been made employing phenylhydrazine concentrations lower than 5.0×10^{-2} *M*; second-order rate constants could therefore be determined directly from observed rate constants and the concentration of phenylhydrazine free base.

The dehydration reaction for all the benzaldehydes is susceptible to specific acid catalysis from pH 5 to 9 (Figure 1). For *p*-chlorobenzaldehyde, benzaldehyde, and *p*-methoxybenzaldehyde, a pH-independent reaction is observed above pH 9 and for *p*-nitrobenzaldehyde both a pH-independent and a specific base-catalyzed reaction are observed (Figure 1). The appropriate rate constants are collected in Table V.

TABLE V

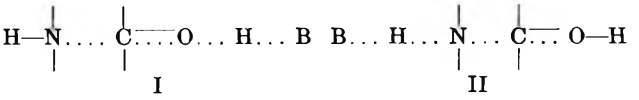
CATALYTIC CONSTANTS FOR THE HYDRATED PROTON, WATER, AND HYDROXIDE ION FOR THE DEHYDRATION OF CARBINOLAMINE INTERMEDIATES IN THE REACTION OF PHENYLHYDRAZINE WITH SEVERAL BENZALDEHYDES IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50

Benzaldehyde	k_{H^+}, M^{-2} min^{-1}	k_{H_2O}, M^{-1} min^{-1}	k_{OH^-}, M^{-2} min^{-1}
p-Nitrobenzaldehyde	4.5×10^8	0.40	4.0×10^2
p-Chlorobenzaldehyde	3.0×10^8	0.44	
Benzaldehyde	2.4×10^8	0.25	
p-Methoxybenzaldehyde	7.0×10^7	0.088	
p-Hydroxybenzaldehyde	3.0×10^7		

Discussion

A. Attack Reaction.—Several arguments have been presented previously to the effect that general acid catalysis of the addition of nitrogen nucleophiles to carbonyl compounds occurs with true general acid catalysis (transition state I) rather than with specific acid–general base catalysis (transition state II).[3,4,6,8,15-17]

(15) C. G. Swain and J. C. Worosz, *Tetrahedron Lett.*, 3199 (1965).
(16) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, **87**, 1553 (1965).
(17) J. E. Reimann and W. P. Jencks, *ibid.*, **88**, 3973 (1966).



I II

Results obtained herein support this conclusion. In the first place a simple calculation based on the experimental third-order rate constant for the hydrated proton-catalyzed attack of phenylhydrazine on *p*-nitrobenzaldehyde (Table I) and the basicity of this aldehyde[18] reveal that the second-order rate constant for attack of the nucleophile on the protonated aldehyde is 9×10^{15} M^{-1} min^{-1} several orders of magnitude larger than rate constants for diffusion-controlled reactions in water.[6,19] Alternate routes to the formation of transition state II appear equally unreasonable as previously developed.[8] Thus, either transition state I must obtain or the reaction must proceed by a "single-encounter" mechanism. Variants of I in which proton transfer occurs through intervening water molecules and the like are, of course, not excluded.

In the second place, the variation of the values of ρ^+ with the acidity of the general acid catalyst (Figure 3) together with considerations concerning variation in transition state structure as function of reactivity[20-23] support transition state I. Specifically, one expects that with increasingly strong acid catalysts this transition state will be reached progressively earlier along the reaction coordinate, consistent with the observation of decreasing values of ρ^+ with increasing acid strength in the catalysts (Figure 3). In contrast, transition state II would predict the opposite since as the strength of the acid catalyst increases the basicity of the conjugate base necessarily decreases. One would expect the transition state to be reached later with the weaker general base catalyst and, hence, that the ρ^+ values would change in the opposite way. In general, both the magnitude and trend of the values of ρ^+ for corresponding reactions for semicarbazone and phenylhydrazone formation from benzaldehydes are similar[6] suggesting similar catalytic pathways. The observation that the rate constants for both water and the hydrated proton fall near the lines in the Brønsted plots constructed from the data for catalysis by carboxylic acids suggests that a common catalytic pathway is employed by all.

The variation in ρ^+ with pK_a of the general acid catalysts can be treated quantitatively. Since the data may be correlated by both Hammett and Brønsted equations, it is easy to show that the following relationship should exist.[6,24]

$$\frac{pK_{a_2} - pK_{a_1}}{\rho_2^+ - \rho_1^+} = C_1 = \frac{\sigma_i}{\alpha_0 - \alpha_i} \qquad (4)$$

Data in Table IV provide a test of former part of this equation which asserts that on changing the catalyst, change of ρ^+ is linearly related to the pK_a of the acid employed as catalyst. Taking the data for the hydrated proton catalysis as standard, a plot of ρ^+ against pK_a has been constructed (Figure 4). Clearly a satis-

(18) K. Yates and R. Stewart, *Can. J. Chem.*, **37**, 664 (1959).
(19) M. Eigen and L. de Maeyer, "The Structure of Electrolytic Solutions," W. J. Hamer, Ed., Wiley, New York, N. Y., 1959, p 64.
(20) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).
(21) J. E. Leffler, *Science*, **117**, 340 (1953).
(22) C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **84**, 817 (1962).
(23) E. R. Thornton, *ibid.*, **89**, 2915 (1967).
(24) S. I. Miller, *ibid.*, **81**, 101 (1959).

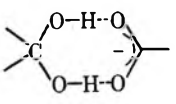
factory straight line is obtained. The slope of the line yields a value of C_1 of 50. This value of C_1 requires that the value of ρ^+ vary only slightly as a function of pK_a in accord with the experimental observations in this work. Specifically, it is predicted that a change of 1.0 in pK_a will cause only a change of 0.02 in ρ^+.

The observed values of α, near 0.35, while small, are considerably greater than those observed for benzaldehyde semicarbazone and thiosemicarbazone formation[6,7] and are larger than expected on the basis of a relationship between α and the pK_a of the nucleophilic reagent.[8] Why the value of α for phenylhydrazone formation should be so large is not completely clear. A very recent observation may, however, require some modification in interpretation of Brønsted exponents for general acid catalysis of carbonyl addition reactions. Specifically, the ratio of rate constants for addition of nucleophiles to benzaldehyde and benzaldehyde-*1-d* is near the theoretical upper limit requiring that C–N bond formation be essentially complete in the transition state.[25] Hence, proton transfer reactions involving the tetrahedral intermediates may be at least partially rate determining for these reactions.[26] Were proton transfer to the immediate adduct rate determining, the value of α would necessarily be zero. Perhaps the actual value observed is principally a reflection of the extent to which proton transfer is rate determining.

A particularly puzzling observation concerning addition of phenylhydrazine to benzaldehydes is the nonlinearity of plots of buffer concentration against rate constants when employing the *p*-nitro aldehyde as substrate (Figure 2). Similar observations have been made previously and reflect a transition to rate-determining carbinolamine dehydration.[6,7] As developed in the Experimental Section, correcting the observed rate constants in the present case to account for the importance of the rate of dehydration has little effect on these constants in the present case. Note specifically that the apparent limiting rate constant with increasing acetate buffer concentration shown in Figure 2 is about an order of magnitude less than that expected for rate-determining dehydration of the carbinolamine. Hence an alternative explanation must be found for this case.

B. Carboxylate Inhibition of Phenylhydrazone Formation.—Having eliminated one possible cause of carboxylate ion inhibition for phenylhydrazone formation from *p*-nitrobenzaldehyde, we are left with that one developed in the Results section: formation of an unreactive complex between substrate and inhibitor. In addition to accounting for the observed inhibition quantitatively, complex formation seems reasonable on the grounds that only the most electrophilic of the substrates experiences such inhibition and that the more nucleophilic carboxylate ions are the better inhibitors.

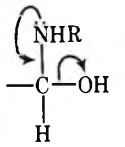
One difficulty with the concept of complex formation is the structure of that complex. Carboxylate ions are known to complex with hydrates of certain aliphatic aldehydes,[27] probably through hydrogen bond formation.



From available information concerning equilibrium constants for the addition of nucleophiles to benzaldehydes,[28] the possibility of direct addition of carboxylate ions to the *p*-nitrobenzaldehyde seems exceedingly remote. At any event, complexation, if it does occur, does not result in a detectable alteration in the ultraviolet absorption spectrum of the aldehyde.

C. Carbinolamine Dehydration.—The dehydration of the carbinolamines formed from the addition of phenylhydrazine to the substituted benzaldehydes is subject to strong acid catalysis and the rates are only slightly sensitive to the nature of polar substituents (Table V). In both regards, the results are typical for reactions of this type.[6,29-31]

The observation of pH-independent dehydration reactions appears to be the first direct detection of such a reaction for weakly basic amines. Several such reactions have been observed for the reverse reaction involving Schiff bases derived from strongly basic amines.[32,33] By analogy with the pathway for Schiff base hydrolysis, the pH-independent reaction must occur as follows.



By assuming a dissociation constant for the conjugate acid of the carbinolamine, protonated on oxygen, of 10^3 *M*, the data in Table V permit one to calculate that the O-protonated carbinolamine expels water about 10^{12} times as rapidly as the neutral species expels hydroxide ion. If the acid-catalyzed and pH-independent reactions are viewed as involving general acid catalysis by the hydrated proton and water, respectively, then the ratio of rate constants is near 5×10^{13} (correcting for the concentration of water in the solvent), fully consistent with the large values of α usually associated with carbinolamine dehydration.[7,32]

Base-catalyzed carbinolamine dehydration has been previously observed for semicarbazone and oxime formation.[31] Is it not surprising that such catalysis is most important for the *p*-nitrobenzaldehyde (Figure 1) since the electron-withdrawing capacity of the nitro group will diminish the capacity of the unshared pair on nitrogen to expel the leaving hydroxide group. Hence, removal, or partial removal, of the proton on nitrogen provides important additional driving force for the reaction and causes the base-catalyzed pathway to be important.

Registry No.—Benzaldehyde phenylhydrazone, 588-64-7; phenylhydrazine, 100-63-0; *p*-nitrobenzaldehyde, 555-16-8; *p*-chlorobenzaldehyde, 104-88-1; benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *p*-hydroxybenzaldehyde, 123-08-0.

Acknowledgment.—The author is indebted to Dr. Eugene H. Cordes for helpful comments concerning this work.

(25) L. do Amaral, H. Bull, and E. H. Cordes, unpublished observations.
(26) R. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 6758 (1969).
(27) L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5224 (1963); *Aust. J. Chem.*, **18**, 1299 (1965).
(28) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).
(29) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).
(30) J. E. Reimann and W. P. Jencks, *ibid.*, **88**, 3973 (1966).
(31) R. Wolfenden and W. P. Jencks, *ibid.*, **83**, 2763 (1961).
(32) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).
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Hückel Molecular Orbital π Resonance Energies. The Nonalternant Hydrocarbons

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The resonance energies and resonance energies per π electron (REPE) have been calculated for 92 nonalternant hydrocarbons. An excellent correlation between REPE and the chemical behavior of the known compounds has been found. A new class of aromatic nonalternant hydrocarbons is proposed, the azulenoids, which consist of two or more fused azulene units. Examples of the azulenoids are compounds **49**, **51**, and **65**.

We have recently introduced a new method of obtaining π resonance energies of cyclic conjugated hydrocarbons using the simple Hückel molecular orbital technique.[1] Empirical π-bond energies were obtained from a series of acyclic polyolefins (a total of eight π-bond energies), and these are used in an additive fashion to obtain the π energy of the hypothetical "localized"[2] structure of a cyclic polyolefin. The difference between the HMO π energy and the additive "localized" energy of a cyclic polyolefin is defined as the resonance energy. Dividing this by the number of π electrons gives the resonance energy per π electron (REPE), a quantity that correlates well with experimental aromaticity. Molecules with a positive REPE (in units of β) are aromatic; those with REPE = 0 are nonaromatic, that is they behave like polyolefins; and those with negative REPE are antiaromatic.[3] We have successfully applied this method to a wide variety of benzenoid hydrocarbons.[4] Unlike HMO delocalization energies, REPE appears to be equally successful in the prediction of aromaticity of both alternants and nonalternants.

In the above we have followed Dewar's definition of aromaticity,[2] except that we have computed energies by the simple HMO method rather than by the more elaborate Pariser–Parr–Pople technique. It is interesting that the simpler method appeared to give slightly better results.[4] In part to test the generality of this observation, we examine in the present paper 92 completely conjugated nonalternants containing four-, five-, six-, and seven-membered rings. The classification proposed by Zahradník has been followed.[5] Should the simpler method continue to perform as well as the more complex, it can be used exclusively with considerable savings in computer time and cost, but, more important, results of the simpler method should be more easily analyzable in any attempt to determine the physical basis of aromaticity.

Our statement that REPE correlates well with experimental aromaticity requires some comment. There is in fact no quantitative experimental measure of "aromaticity." There is only a qualitative idea that aromatic compounds should be unusually stable, and that typically they should undergo substitution rather than addition reactions. We observe that in fact compounds with positive REPE usually are stable and do react by electrophilic substitution; the greater the REPE, the more true this is. Compounds with REPE = 0 are like polyolefins; they are not especially stable; and they react by addition. Compounds with negative REPE usually have not been synthesized or exist only fleetingly. We have not shown why this correlation should exist; we have only noted that it does exist. When we find exceptions, such as a compound computed to have a large REPE but for which synthetic attempts have failed, there are usually found to be easy conversion routes to another with still higher REPE. Since our definition of aromaticity is only qualitative, we can have only a qualitative correlation of aromaticity and REPE, but the point is that even this qualitative correlation is much superior to anything achieved with such earlier theoretical parameters as delocalization energy.

Results and Discussion

Total π energies, additive "localized" energies, resonance energies (RE), and resonance energies per π electron (REPE) are tabulated for compounds **1**–**92** in Table I. In addition, those for which either the parent compound or simple derivatives have been isolated (i) or observed in solution (s) are indicated. In a number of cases more than one localized structure can be drawn for a compound. The average of these energies, which never differ significantly, was used.[4]

A. Bicyclic.—Of the three possible bicyclic nonalternants (excluding ions or radicals) only azulene (**2**) has appreciable resonance energy. In agreement with this is its chemical behavior which is well known to be that of an aromatic hydrocarbon. Heptalene (**3**) with a slightly negative resonance energy should behave as a reactive polyolefin as is found to be the case. Dauben has reported its preparation in solution but found it to be too reactive to be isolated.[6] Pentalene with a high negative resonance energy has never been prepared despite numerous attempts. The success of the correlation of REPE with the chemical stability of these three bicyclics might be contrasted to the lack of correlation between delocalization energy and stability. The delocalization energies per π electron (DEPE) for **1**–**3** are 0.307, 0.336, and 0.302 β, respectively. Note that pentalene has a higher DEPE than does heptalene which is just the opposite of their known chemical behavior and their REPE's.

B. Tricyclic (Kata Condensed).—Only two of the 15 kata-condensed tricyclics **4**–**18** have significant resonance stabilization, cyclohept[*f*]indene (**15**) and cyclohept[*e*]indene (**16**). Neither has been prepared al-

(1) B. A. Hess, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.*, **93**, 305 (1971).

(2) (a) M. J. S. Dewar and C. de Llano, *ibid.*, **91**, 789 (1969); (b) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969.

(3) R. Breslow, *Chem. Eng. News*, **43**, 90 (1965).

(4) B. A. Hess, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.*, **93**, 2413 (1971).

(5) R. Zahradník and J. Michl, *Collect. Czech. Chem. Commun.*, **30**, 515 (1965).

(6) H. J. Dauben, Jr., and D. J. Bertelli, *J. Amer. Chem. Soc.*, **83**, 4659 (1961).

TABLE I
HÜCKEL π ENERGIES AND RESONANCE ENERGIES OF NONALTERNANT HYDROCARBONS IN UNITS OF β

Compd	Hückel	Additive	RE	REPE	Status[a]	Compd	Hückel	Additive	RE	REPE	Status[a]
1	10.456	10.596	−0.141	−0.018	—	47	24.455	24.236	0.219	0.012	—
2	13.364	13.132	0.231	0.023	i	48	24.511	24.236	0.275	0.015	—
3	15.618	15.668	−0.050	−0.004	s	49	24.595	24.236	0.359	0.020	—
4	13.309	13.612	−0.302	−0.030	—	50	24.522	24.208	0.314	0.017	—
5	13.416	13.640	−0.224	−0.022	—	51	24.583	24.208	0.375	0.021	—
6	15.872	16.148	−0.276	−0.023	—	52	24.529	24.236	0.293	0.016	—
7	15.889	16.120	−0.231	−0.019	—	53	22.210	21.700	0.510	0.032	—
8	15.870	16.148	−0.277	−0.023	—	54	24.745	24.236	0.509	0.028	—
9	16.203	16.176	0.027	0.002	—	55	21.959	21.697	0.262	0.016	—
10	16.231	16.121	0.110	0.009	i	56	22.036	21.699	0.337	0.021	—
11	15.899	16.148	−0.249	−0.021	—	57	22.063	21.725	0.338	0.021	—
12	18.413	18.656	−0.243	−0.017	—	58	24.595	24.233	0.362	0.020	—
13	18.395	18.684	−0.289	−0.021	—	59	24.396	24.235	0.161	0.009	—
14	18.533	18.711	−0.178	−0.013	—	60	24.525	24.261	0.264	0.015	—
15	18.894	18.657	0.237	0.017	—	61	16.194	16.626	−0.432	−0.036	—
16	19.038	18.684	0.354	0.025	—	62	19.128	19.162	−0.034	−0.002	—
17	21.338	21.193	0.145	0.009	—	63	19.280	19.162	0.118	0.008	—
18	21.097	21.220	−0.123	−0.008	—	64	22.030	21.698	0.332	0.021	—
19	12.995	13.610	−0.615	−0.062	—	65	22.051	21.698	0.353	0.022	i
20	16.366	16.146	0.220	0.018	i	66	21.949	21.698	0.251	0.016	i
21	16.619	16.146	0.473	0.039	i	67	24.401	24.234	0.167	0.009	i
22	18.911	18.682	0.229	0.016	i	68	24.298	24.234	0.064	0.004	—
23	19.145	18.682	0.463	0.033	i	69	26.552	26.770	−0.218	−0.011	—
24	20.913	21.218	−0.305	−0.019	—	70	19.426	19.162	0.254	0.018	s
25	18.749	19.164	−0.415	−0.030	—	71	19.410	19.164	0.246	0.018	—
26	19.097	19.164	−0.067	−0.005	—	72	19.494	19.162	0.332	0.024	—
27	21.890	21.646	0.244	0.015	—	73	22.252	21.698	0.554	0.035	i
28	21.749	21.673	0.076	0.005	—	74	21.993	21.700	0.293	0.018	—
29	21.745	21.700	0.045	0.003	—	75	22.206	21.698	0.508	0.032	i
30	21.757	21.700	0.057	0.004	—	76	22.220	21.698	0.522	0.033	i
31	29.144	29.252	−0.108	−0.005	—	77	24.533	24.234	0.299	0.017	—
32	29.336	29.252	0.084	0.004	—	78	24.537	24.236	0.301	0.017	—
33	29.151	29.280	−0.129	−0.006	—	79	24.608	24.234	0.374	0.021	—
34	29.343	29.280	0.063	0.003	—	80	35.666	35.285	0.381	0.015	—
35	29.122	29.308	−0.186	−0.008	—	81	46.807	46.361	0.446	0.013	—
36	29.347	29.308	0.039	0.002	—	82	57.948	57.437	0.511	0.012	—
37	24.220	24.208	0.012	0.001	—	83	69.089	68.514	0.574	0.011	—
38	24.381	24.208	0.173	0.010	—	84	35.782	35.285	0.497	0.019	—
39	24.402	24.236	0.166	0.009	—	85	46.982	46.361	0.621	0.018	—
40	24.238	24.236	0.002	0.000	—	86	58.180	57.437	0.743	0.018	—
41	24.553	24.236	0.317	0.018	—	87	69.378	68.514	0.864	0.017	—
42	24.473	24.208	0.265	0.015	—	88	35.822	35.284	0.538	0.021	—
43	24.503	24.180	0.323	0.018	—	89	47.064	46.360	0.704	0.021	—
44	24.445	24.180	0.265	0.015	—	90	58.305	57.435	0.870	0.021	—
45	24.528	24.208	0.320	0.018	—	91	69.547	68.511	1.036	0.021	—
46	24.502	24.236	0.266	0.015	—	92	67.455	66.454	1.001	0.021	—

[a] i, isclated; s, observed in solution; —, unknown.

though attempts at the synthesis of **15** have been made.[7] Bertelli[7b] thought that the failure of his attempted synthesis of a simple derivative of **15** was due either to the high reactivity of **15** because of its potential facile conversion to a benzenoid aromatic system by reaction with its environment or to the fact that it possessed essentially no π-electron delocalization. Our calculations suggest that the inability to isolate **15** is due to the former reason.

Compounds **9**, **10**, and **17** all possess relatively little resonance energy and should behave as polyolefins. The synthesis of *s*-indacene (**10**) has been reported by Hafner and its behavior is that of a polyene.[8] The remainder of the kata-condensed tricyclics have substantially negative REPE's; none have been prepared; and it would appear that further attempts at synthesis would be futile. Examination of the REPE's of **4** and **5** (−0.030 and −0.022 β) which are both π isoelectronic with azulene and which might be conceived of as having cyclic ten-π peripherial systems indicates the danger of applying the Hückel $4n + 2$ rule to other than monocyclic systems.[9]

C. Tricyclic (Peri Condensed).—Compounds **20**–**23** possess a significant amount of resonance energy as indicated by their high REPE's. The parent hydrocarbons **21** and **23**[10] and a dimethyl derivative of **22**[11] are known and exhibit normal aromatic behavior. A dimethyl derivative of **20** has been reported.[12] Com-

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(8) K. Hafner, K. H. Häfner, C. König, M. Kreuder, G. Ploss, G. Schulz, E. Sturm, and K. H. Vöpel, *Angew. Chem., Int. Ed. Engl.*, **2**, 123 (1963).

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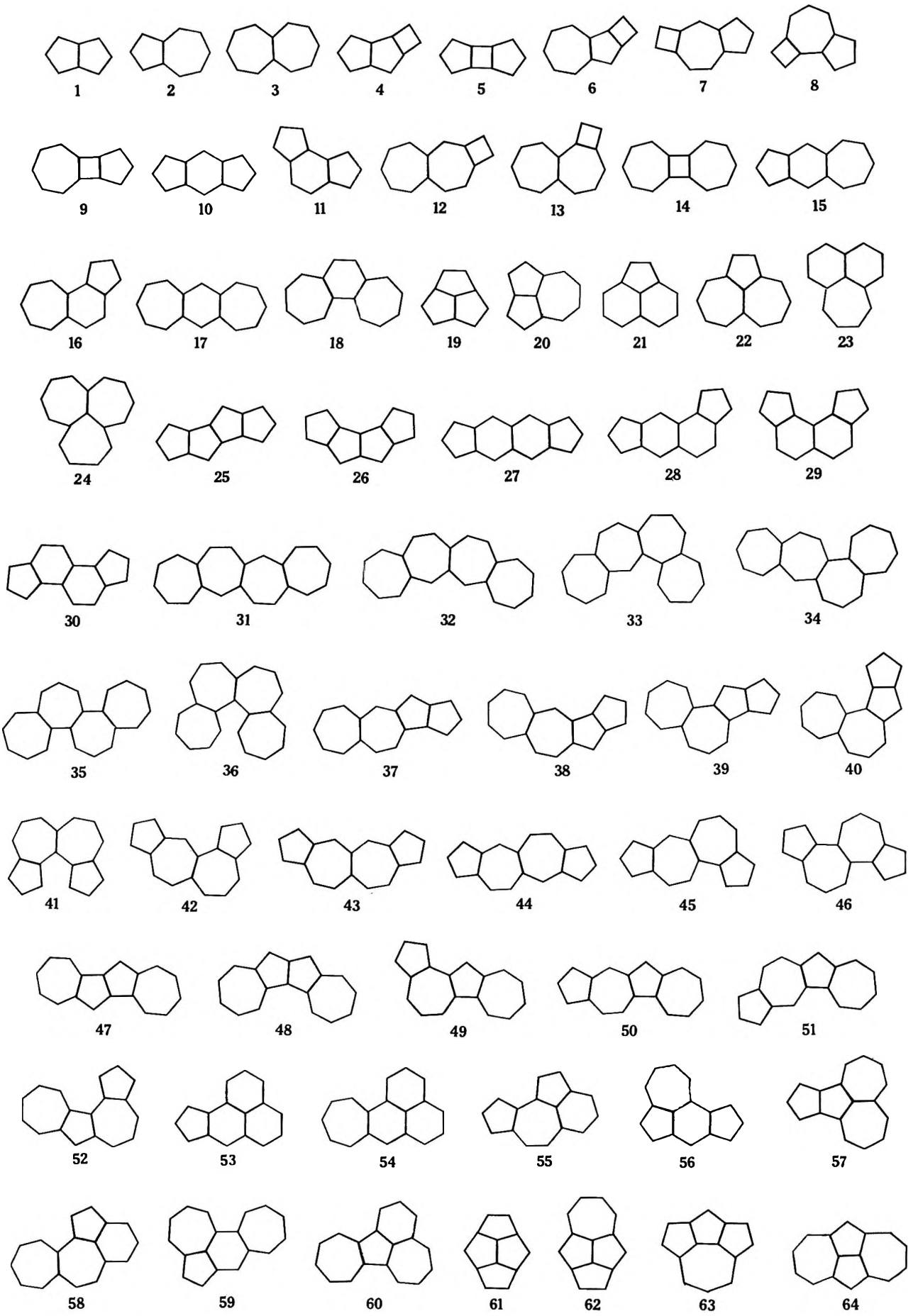
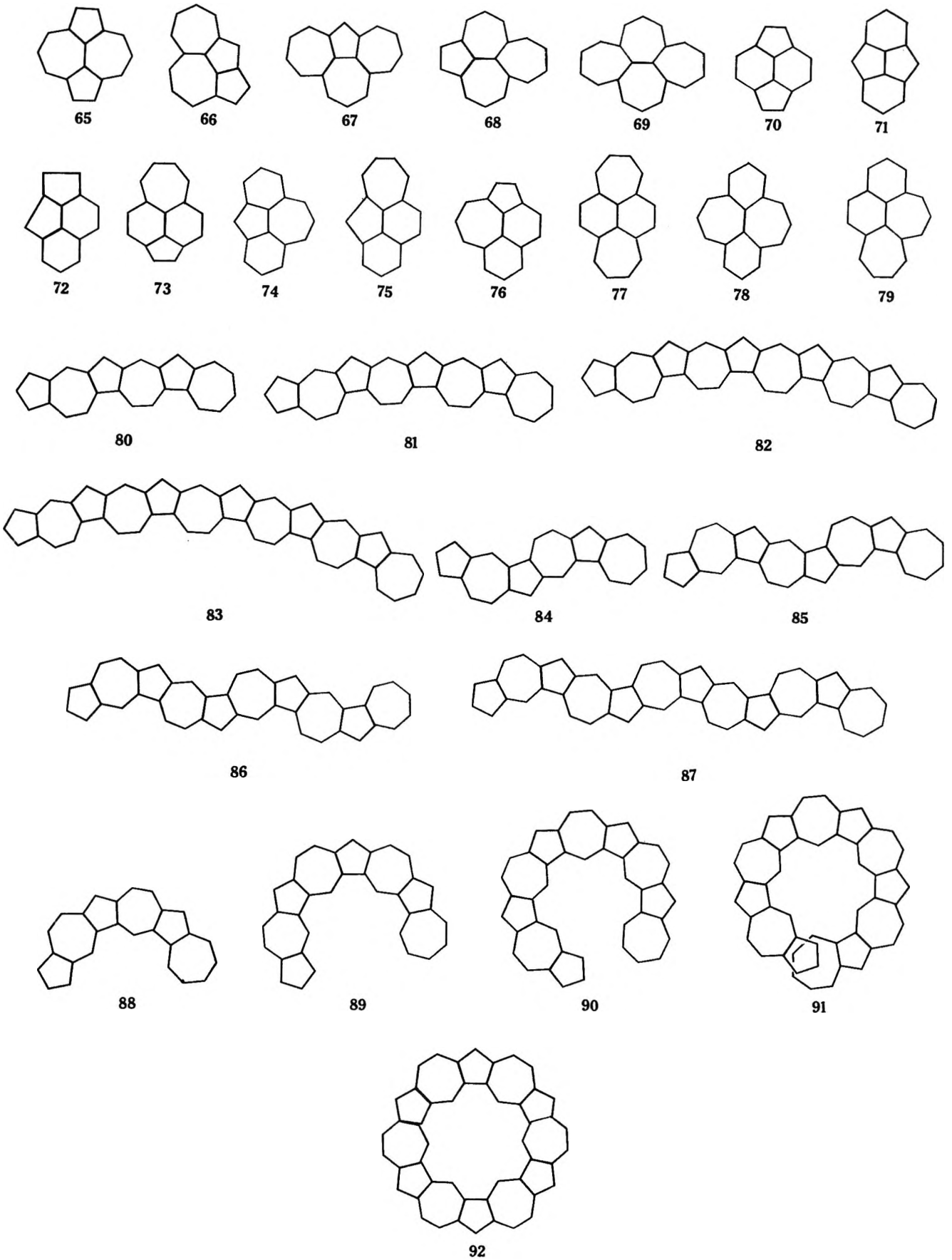


pound **20** does not behave as an aromatic hydrocarbon but as a polyolefin since it readily undergoes reaction with dienes and dienophiles. Hafner attributes its reactivity to angle strain and its ability to form the azulene system. The remaining two tricyclics **19** and **24** are predicted to be antiaromatic. Neither has been isolated.

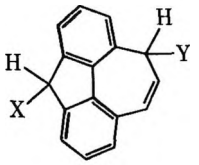


D. Tetracyclic (Kata Condensed).—One conclusion may be immediately made about the kata-condensed tetracyclics. Usually only those compounds which consist of two fused azulene units (**41**–**52**) appear to be potentially aromatic and therefore isolable. Compound **27** is not of this type but also is predicted to have significant resonance stabilization. However, potential conversion to a benzenoid system makes its isolation questionable. There is a remarkable constancy in the REPE's of **41**–**52**. They all fall between +0.015 and +0.021 β with the exception of **48**. Furthermore, all potential conversion products would be simple azulene

derivatives. Since azulene has only a slightly higher REPE, these compounds all appear to be potentially stable aromatic systems (see further discussion below). None have yet been prepared.

E. Tetracyclic (Kata–Peri Condensed).—Compounds **53–60** all have significant positive REPE's with the exception of **59** and hence appear to be good candidates for aromatic systems. None have been reported, but a benz derivative of **53** has been reported to possess aromatic properties much like azulene.[13] Zahradník has previously examined the potential aromaticity of these compounds and has arrived at similar conclusions.[14] His conclusions were based mainly on specific delocalization energies (DE_{sp}); these are obtained by dividing delocalization energy by the number of C–C bonds. Although DE_{sp} correlates quite well with REPE and therefore aromaticity for compounds of similar structure and size (*e.g.*, a good linear relation is found between DE_{sp} and REPE of the 14-π tetracyclic systems in Table I), the correlation when systems of differing size and structure are considered is quite poor. For example, while hexatriene, trimethylenecyclopropane, fulvene, heptafulvene, and heptalene all have essentially the same HMO REPE[1] (all are predicted to be nonaromatic), their DE_{sp} vary from 0.198 β for hexatriene to 0.278 β for heptalene, which is a considerably greater variation than is found between benzene (DE_{sp} = 0.333 β) and azulene (DE_{sp} = 0.306 β).

F. Tetracyclic (Peri Condensed).—Three compounds in this group have an REPE greater than +0.030 β: **73, 75,** and **76**. Their high REPE may be due partially to the presence of the naphthalene system in all three. All have been prepared and possess typical aromatic properties.[11,15,16] Of the remaining compounds a large number possess significant REPE (**64–66, 70–72, 74, 77–79**). The parent hydrocarbons **65** and **70** and methyl derivatives of **66** and **67** have been prepared.[17–20] Several attempted syntheses of **74** have failed.[21] Although **74** does possess significant REPE (0.018 β), its potential conversion to the biphenyl (**93**)



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by addition across the azulene system may make it a rather reactive system. It has also been noted that **74** may possess a triplet ground state.[22]

Trost has recently reported the synthesis and properties of pyracyclene (**70**).[20] Although pyracyclene is stable in solution it cannot be isolated and, in general, exhibits a rather low stability. We suggest that its low stability may be due to its potential conversion to the more highly aromatic acenaphthylene system (+0.039 β). Trost's argument for the antiaromaticity of pyracyclene may be incorrect since he bases it mainly on the nmr spectrum of **70**. The use of nmr chemical shifts as a criterion for aromaticity has been seriously questioned.[23]

Both **61** and **69** are significantly antiaromatic, and neither has been prepared. Garratt and Sargent have suggested that since **61** has a $4n + 2$ periphery, it might be a good candidate for attempted synthesis.[24] Again we see the danger of applying Hückel's rule to polycyclic systems. For **61** we calculate an REPE of −0.036 β, which certainly will make this system antiaromatic.

Zahradník has computed a "stability index" for compounds **61–79**.[25] This index correlates reasonably well with REPE. However, it is based partially on DE_{sp} and therefore its use is limited to a series of similar compounds such as the tetracyclic–peri-condensed systems.

H. Larger Systems.—The very similar REPE's of **41–52** suggested to us the possibility that larger ring systems containing three or more fused azulene units might produce stable aromatic nonalternant hydrocarbons. We therefore examined several series of alternating five- and seven-membered rings, **80–83, 84–87,** and **88–91**. The REPE's of the first series **80–83** drop well below the value of azulene (+0.023 β) as the number of rings increases, suggesting increased reactivity as the number of rings increases. This behavior is similar to that of the linear polyacenes where REPE falls quite drastically as the number of rings is increased in the naphthalene, anthracene .... series.[4] However, in the case of the second series, **84–87,** the REPE falls only slightly with increase in the number of rings. These potentially form a new series of stable aromatic nonalternants. The behavior of REPE in this series is again similar to that of a polyacene series, naphthalene, phenanthrene, chrysene .... in which the REPE falls off only slightly as the number of rings increases.[4] Even more striking is the constancy of the REPE in the third series **88–91**.

These observations suggested to us that nonalternants composed of two or more fused azulene units may well represent a new class of nonalternant aromatics for which we suggest the name azulenoids. For example, we predict that compounds **49, 51,** and **88** should possess aromatic properties very much like those of azulene.

In conclusion we again emphasize that a positive REPE of a compound is not necessarily the only requirement for chemical stability but possible conversion paths to more stable products must also be considered (*e.g.*, compound **70** as discussed above).[26]

Registry No.—**1,** 250-25-9; **2,** 275-51-4; **3,** 257-24-9; **4,** 26223-08-5; **5,** 253-01-0; **6,** 31151-50-5; **7,** 31151-51-6; **8,** 31151-52-7; **9,** 7001-11-8; **10,** 267-21-0; **11,** 210-65-1; **12,** 13375-70-7; **13,** 13375-69-4; **14,** 257-53-4; **15,** 270-19-9; **16,** 235-43-8; **17,** 259-63-2; **18,** 229-21-0;

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19, 187-68-8; **20**, 209-86-9; **21**, 208-96-8; **22**, 209-42-7; **23**, 208-20-8; **24**, 4325-69-3; **25**, 13357-37-4; **26**, 13357-31-8; **27**, 257-56-7; **28**, 388-79-4; **29**, 31151-71-0; **30**, 217-04-9; **31**, 31151-73-2; **32**, 31180-51-5; **33**, 31151-74-3; **34**, 31151-75-4; **35**, 31151-44-7; **36**, 31151-45-8; **37**, 31141-14-7; **38**, 31141-15-8; **39**, 31141-16-9; **40**, 31141-17-0; **41**, 31141-18-1; **42**, 31141-19-2; **43**, 31141-20-5; **44**, 31141-21-6; **45**, 31141-22-7; **46**, 31141-23-8; **47**, 31141-24-9; **48**, 31141-25-0; **49**, 31141-26-1; **50**, 31141-27-2; **51**, 31141-28-3; **52**, 31141-29-4; **53**, 211-95-0; **54**, 20542-67-0; **55**, 20542-69-2; **56**, 20542-70-5; **57**, 31133-53-6; **58**, 5695-16-9; **59**, 4429-72-5; **60**, 20542-74-9; **61**, 569-40-4; **62**, 22719-10-4; **63**, 22719-09-1; **64**, 3526-04-3; **65**, 193-85-1; **66**, 781-30-6; **67**, 436-86-2; **68**, 22719-08-0; **69**, 22874-06-2; **70**, 187-78-0; **71**, 13357-45-4; **72**, 203-72-5; **73**, 194-32-1; **74**, 203-57-6; **75**, 203-71-4; **76**, 194-23-0; **77**, 193-90-8; **78**, 192-29-0; **79**, 31180-48-0; **80**, 31141-54-5; **81**, 31141-55-6; **82**, 31141-56-7; **83**, 31141-57-8; **84**, 31141-58-9; **85**, 31141-59-0; **86**, 31141-60-3; **87**, 31141-61-4; **88**, 31152-32-6; **89**, 31152-33-7; **90**, 31152-36-0; **91**, 31152-34-8; **92**, 31152-35-9.

Cobalt-60 Radiation-Initiated Oxidation of Hydrocarbons in Emulsion[1]

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Aqueous emulsions of a variety of hydrocarbons under cobalt-60 irradiation have been allowed to react with molecular oxygen at pressures of 1–4 atm at 50°. Unlike the effect observed in polymerization, emulsification of styrene had no significant effect on the oxidation rate or products as compared to that observed in hydrocarbon solution. With emulsions of styrene and α-methylstyrene, dependency on the rate of initiation and temperature is consistent with the bulk mechanism, and the product distribution qualitatively parallels bulk oxidations. Other hydrocarbons investigated include cyclohexene, cyclopentene, tetramethylethylene, tetralin, and cumene. The efficiency of initiation by radiation varied from 10 to 40%.

The effect of emulsification on the oxidation of hydrocarbons has received attention from a number of researchers, largely in the hope of finding an increase in the kinetic chain length or variation in products. The information available at the start of our program was inadequate to tell what the effect of emulsification was on any oxidation process. For example, studies have been made on methyl oleate,[3] methyl linoleate,[4] aldehydes,[5] cumene,[6] and 1,1-diphenylethylene,[6] but in these cases all experiments were performed without controlled initiation. Thus a comparison of rate with that in solution is not possible. The literature also contains many other articles reported in a phenomenological manner which contribute little to the understanding of emulsion oxidation.

Recently Hyde and Verdin[7] have reported on the effect of emulsification on the radiation-induced oxidation of methyl oleate under controlled conditions. Although hydroperoxide is formed quantitatively in the initial stages of the reaction in both emulsion and bulk, the yield of the hydroperoxide decreases more rapidly with conversion in the emulsion system than in bulk. The rate of emulsion oxidation, based on the amount of methyl oleate present, is increased up to a factor of 5.8 over the bulk rate. This increase is attributed to an increase in initiation rate and not to an enhancement in chain length. Apart from this small enhancement of rate, the reaction kinetics seem similar to those of the homogeneous system.

Using emulsion polymerization[8-12] as a model for emulsion oxidation one might expect that emulsification should cause rate enhancement. Briefly, the theory of emulsion polymerization[13,14] has utilized the concept of isolation of the chain carriers in the soap micelle or polymer particle, thereby preventing termination. Further rate enhancement occurs due to the high viscosity of the growing particle,[12] which retards diffusion-controlled termination within the particle even after another chain carrier enters the particle. Since the oxidation of hydrocarbons also follows a free-radical mechanism,[15,16] emulsification is expected to have an effect if the concept of isolation of the growing chain carriers is important. If the high viscosity of growing particles is the main factor which causes enhancement of rate in emulsion polymerization, then enhancement would be expected to be small in cases where the product is of a low molecular weight such that there is little change in the viscosity of the particle with conversion. In the oxidation of olefins which form alternating copolymers with oxygen, there may be sufficient changes in viscosity so that some rate enhancement might be expected to occur. There is only a limited amount of data on the emulsion oxida-

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(16) See, for example, C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, p 418.

tion of such compounds and then only for styrene,[17,18] where the results appear similar to that observed in bulk.[19,20] Thus our objective in studying emulsion oxidation has been directed largely, although not entirely, to the reaction of olefins which form polymeric products.

Most of the reactions have been initiated by γ radiation from cobalt-60. This source of initiation has distinct advantages over chemical initiation, as has been demonstrated in its use in emulsion polymerization.[21,22] Among the advantages are a constant and easily attenuated source of initiation and lack of chemical contamination.

Experimental Section

Materials.—Reactants and emulsifiers were obtained through the following sources: styrene, α-methylstyrene, cetyltrimethylammonium bromide (CTABr) and chloride (CTACl), *N*,*N*-bis(2-hydroxyethyl)dodecanamide (BHD), azobisisobutyronitrile, and cetylpyridinium chloride (CPC) from Eastman Organic Chemicals; cyclohexene, tetralin, cumene, acetaldehyde, potassium persulfate, and sodium lauryl sulfate (NaLS) from Matheson Coleman and Bell; cyclopentene and butadiene from Phillips Petroleum; tetramethylethylene from Aldrich; poly(oxyethylene) palmitate (POEP) from Atlas Chemical Industries; sodium laurate (NL) from Baker Chemical; methyl methacrylate from Rohm and Haas. *N*-(2-Diethylaminoethyl)palmitamide (P) was prepared from palmitoyl chloride and *N*,*N*-diethylethylenediamine and converted to the hydrochloride by treatment with hydrochloric acid. Hydrocarbons were distilled prior to use.

Apparatus.—Most oxidation and polymerization reactions were carried out in a thermostated bath constructed of $^3/_{16}$-in. sheet aluminum, which was placed by an aluminum window adjacent to one position of the cobalt-60 source. The reaction bulbs were clamped to the arm of a wrist action shaker so that when the source was in position the bulbs were at the position of maximum dose rate.

The reaction bulb was connected by Swagelok fitting (Nylon ferrules) to a valve joined by 20 ft of $^1/_{16}$-in. stainless steel tubing to an oxygen supply tank and pressure gauge located behind the radiation shield at ambient temperature. The total volume of the oxygen supply tank and connections to the valve was 42.5 ml. The volume (total) of the reaction bulb most commonly used was 160.5 ml. The radiation dose delivered to the bulbs was determined by ferrous sulfate dosimetry.

Procedure.—Emulsions were made up by dissolving the desired amount of emulsifying agent in 180 ml of water, then adding the desired amount of organic substrate to the soap solution and homogenizing the mixture in a high-speed blender for 1 min. The emulsion was poured into a capped jar to allow the foam to settle, and then 100 ml of the emulsion was delivered to the reaction bulb by hypodermic syringe; the bulb was weighed (to 1 mg) and then attached to the Swagelok fitting. If a polymerization rather than oxidation was to be followed, the bulb was capped with a serum stopper (rather than the fitting) so that samples could be withdrawn by a long hypodermic needle and syringe. Manipulation of an apparatus of this type has been described previously.[23] To avoid breaking emulsions no freeze–thaw degassing was carried out.

Calculations.—The pressure readings made at the ambient tank temperatures were corrected to 27° by the following equation

$$P_{27^\circ} = \frac{(14.7 + P_1)300.16}{(T_1 + 273.16)} Z$$

$$Z = \frac{V_1T_2 + V_2(273.16 + T_1) + RS(273.16 + T_1)T_2V_3}{V_1T_2 + V_2(300.16) + RS(300.16)T_2V_3}$$

where P_{27° is the corrected reading in psi absolute, P_1 is the measured pressure in psig, and T_1 is the ambient temperature. T_2 is the reaction temperature (of the bulb); V_1, V_2, and V_3 are the volumes of the apparatus (42.5 ml), void space in bulb (usually 60 ml), and emulsion volume (usually 100 ml); and R and S are the gas constant (0.08205 l. atm deg^{-1} mol^{-1}) and the solubility of oxygen in the emulsion, taken to be 15×10^{-4} mol l.$^{-1}$ atm^{-1} for most of the emulsions (styrene, 10% in water). The data were processed using a BASIC computer program and General Electric time-sharing computer service. Oxidation rates were calculated as described previously.[23]

Product Analysis.—In some oxidations, where polyperoxide and carbonyl compounds from substrate cleavage were present, products were isolated by delivering the 100-ml emulsion into 350 ml of methanol and allowing the mixture to stand in the refrigerator. The polymer settled out and the supernatant liquid was decanted and saved for glpc analysis. The polymer was redissolved in benzene and reprecipitated twice with methanol, then freeze-dried in benzene solution. The weight of the polymer and, in some instances, the molecular formula and molecular weight were determined.

Where polyperoxide was not expected as a major product, the emulsion was broken by addition of a strong solution of electrolyte, either ammonium sulfate or potassium sulfate, and this mixture was continuously extracted with ether. The ether solution was dried and worked up in a manner previously described[24] for determining products of oxidation of C_5, C_6, and C_7 hydrocarbons.

Results and Discussion

The following discussion of the results given in the tables shows that the kinetics and mechanism of emulsion oxidation much more closely follow bulk oxidation than emulsion polymerization phenomena. The discussion of an interesting "latex effect" (augmentation of oxidation rate of substrates when absorbed in a polymer latex) will be presented elsewhere.[25]

Emulsion Oxidation Rates *vs.* Bulk Rates.—In the following discussion the assumption that bulk oxidations follow the simplified rate expression (eq 1) is made.

$$R_0 = -\mathrm{d}[O_2]/\mathrm{d}t = k_p[RH](R_i/2k_t)^{1/2} \quad (1)$$

Here R_0 or $-\mathrm{d}[O_2]/\mathrm{d}t$ is the rate of oxygen consumption, k_p is the rate constant for the propagation reaction

$$RO_2 + RH \xrightarrow{k_p} \underset{\text{(abstraction)}}{RO_2H} \quad \text{or} \quad \underset{\text{(addition)}}{R\dot{O}_2RH} \quad (2)$$

where [RH] is the concentration of the substrate, R_i the rate of production of radicals in the system, and k_t the rate constant for the radical termination

$$2RO_2 \xrightarrow{k_t} \text{nonradical products} + O_2 \quad (3)$$

Equation 1, which is the simplest possible rate law for typical free-radical chain oxidation, requires that kinetic chain lengths be long and does not allow for complications that may arise,[12] such as nontermination[26] in eq 3. Nonetheless, it is a useful framework in which to discuss our results.

For a comparison of bulk oxidation rates with those observed in emulsion, the composite rate constant of eq 1, $k_p/(2k_t)^{1/2}$, for various substrates has been collected next to the emulsion oxidation rates in Table III. It is apparent that the emulsion oxidation rates parallel the bulk rate only in a qualitative way which depends on

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TABLE I

OXIDATION OF STYRENE EMULSIONS AT 50°

Expt no.	Emulsifying agent, g/l. in aqueous phase[a]	C_8H_8, mmol	Time, min	ΔO_2, mmol	$R_0^b \times 10^4$, initial	$R_0^{b,c} \times 10^4$, final	Other data
		Co-60 Radiation at 200 rad/min					
9056-3	POEP 2.77	87.1			0.72		
44	POEP 5.56	86.3	1409	13.7	1.1	0.4[d]	
130	POEP 5.53	87.8	2511	4.6	<0.05[d]	0.2[d]	First 1154 min to check for initial thermal rate; 1.878 g, $C_8H_{8.28}O_{1.39}$, mol wt ~3500, isolated
139a	POEP 11.5	86.6	~4000	16.0	1.4	1.5	
18	POEP 5.62	87.7	1379	16.7	0.93	1.9	
	NLS 1.47					0.9[d]	
22	POEP[e] 51.1	339.2	435	1.5	0.04[d]	0.24	
					0.16		
69	CTABr 5.56	87.5	1408	9.9	0.9	0.8	
72	CTABr 11.2	~88	1133	5.0	1.0	0.1	Emulsion broken at end of run
102	CTABr 5.7	87.4	1513	6.0	0.58[d]	0.6[d]	
					1.1		
107	CTACl 5.73	86.3	254	10.1	0.42[d]	1.2[d]	
					1.2		
15	CPC 5.57	84.3	2510	7.7	0.40	0.33	
105	NLS 5.88	88.4	395	1.7	0.81	0.2[d]	
79	BHD 5.56	89.4	1219	8.6	1.3	0.8	Emulsion broken at end of run
97	*e* *e*	400	1180	5.0	0.08[d]	0.13[d]	
					0.22		
9216-18	POEP 5.55	87.7	1336	15.9	0.90	1.9	
	NLS 1.42						
9056-53	POEP 5.49	95.7	76	0.0	82[f]		
		$K_2S_2O_8$ Added as Initiator, No Irradiation					
							$K_2S_2O_8$[g] concn, *M*
9056-11	POEP 5.53	88.8	1280	2.7	0.34		0.0011
125	POEP 5.56	84.2	4068	78.7	3.1	2.8[h]	0.0057
110	POEP 5.56	89.8	372	7.7		2.0	0.0110
116	POEP 5.80	85.3	1150	31.5	3.3	3.7	0.0219
139a	POEP 11.5	84.1			1.4		0.0012
b	POEP 11.5	84.1[c]			2.0[c]		0.0023
c	POEP 11.5	84.1[c]			2.9[c]		0.0045
8	POEP 11.0	86.3	400	14.8	4.4	4.4	0.0108
133	POEP 5.6	88.8	187	11.1	7.0	7.0	0.011
	NLS 1.4						
136	POEP 5.53	87.5	1233	47.7	7.0	2.3	0.011
	NLS 2.76						
6	POEP 5.53	89.8	1450	3.4	0.27	0.27	[ABN] = 0.010 in C_8H_8; no $K_2S_2O_8$ in H_2O

[a] POEP = $C_{15}H_{31}COO(CH_2CH_2O)_{20}H$; CTACl = $C_{16}H_{33}N(CH_3)_3Cl$; NLS = $C_{12}H_{25}OSO_3Na$; CTABr = $C_{16}H_{33}N(CH_3)_3Br$; BHD = $C_{11}H_{23}CON(C_2H_4OH)_2$; CPC = $C_{16}H_{33}N(CH)_5Cl$; NL = $C_{11}H_{23}COONa$; P = $C_{15}H_{31}CONHCH_2CH_2NH(C_2H_5)_2Cl$. All runs done with *ca.* 90 ml of H_2O present; O_2 pressures ranged from 1 to 4 atm. [b] Initial and final rates in mol of O_2 per mol of styrene per min. [c] Based on starting quantity of styrene. [d] Thermal rate, no radiation. [e] Neat styrene, no aqueous phase. [f] Rate of polymerization in absence of oxygen. [g] Concentration in the aqueous phase. [h] Average rate from 6 to 83% conversion.

the emulsifying agent. For those hydrocarbons that oxidize by the abstraction process, where hydroperoxide products may augment the initiation, the discrepancies are even more marked.

The last column of Table III, which is reassembled from Tables I and II, gives a value expected to reflect the efficiency of capture of radicals from the aqueous phase by the droplets of the substrate. The number was obtained by calculating R_i from eq 1

$$R_i = \{R_0/[k_p/(2k_t)^{1/2}]\}^2$$

and dividing by the total initiation rate produced by the Co-60 radiation of 200 rads/min. The latter initiation rate for the oil phase, assuming that all radicals formed in the aqueous phase enter the oil phase, is calculated to be 1.0×10^{-5} *M*/min in the case where the volume ratio of water to hydrocarbon is 9 to 1. A value[27] of $G(R\cdot) = 5$ was taken for water, and radicals produced by the direct radiolysis of the hydrocarbon were neglected. Assuming that the value for α-methylstyrene is too low because of transfer, and neglecting the anomalous tetramethylethylene result, capture of radicals by the substrate droplets appears 10–40% efficient where the concentration of emulsifying agent is 6.0 g/l. of H_2O and the volume ratio of substrate to water is 1:9. Since these numbers are calculated from eq 1 derived for the bulk mechanism, they are expected to be on the high side if there is any intrinsic acceleration of oxidation in emulsion. Hyde and Verdin concluded, on the basis of inhibited emulsion oxidation of methyl oleate, that capture of radicals from the aqueous phase was 100% efficient.[7]

(27) T. Balkas, F. S. Dainton, J. K. Dishman, and D. Smithies, *Trans. Faraday Soc.*, **62**, 81 (1966), show for aqueous solutions at most pH values, $G_{OH} + (G_{e_{aq}^-} + G_H) = 5$.

TABLE II

OXIDATION OF HYDROCARBONS IN EMULSION AT 50° Co-60 RADIATION INITIATION (200 RADS/MIN)

Expt no.	Hydrocarbon	Emulsifying agent, g/l.[a]	RH, mmol	ΔO_2, mmol	$R_0 \times 10^4$, initial[b]	$R_0 \times 10^4$, final[b,c]	Other data
9056-113	α-Methylstyrene	CPC 11.1	79.7	3.4	0.78	0.4	Initial thermal rate ~0.09
120	α-Methylstyrene	CPC 11.3	67.4	1.5	0.20	0.1	98.1 mmol of C_6H_6 present
94	α-Methylstyrene	CPC 5.56	77.2	4.7	0.36		
82	α-Methylstyrene	BHD 5.40	75.2	8.6	2.6	0.9	Emulsion broken
9216-65	α-Methylstyrene	POEP 5.53	77.7	12.7	1.2	1.5	
9056-49	Cyclohexene	POEP 5.95	96.8	10.7	0.65	1.3	8.3 mmol of $-O_2H$ formed
65	Cyclohexene	NL 5.12	97.4	11.4	0.14	1.0	
74	Cyclohexene	P 5.6	98.4	5.3	0.15	0.79	
56	Cyclopentene	POEP 6.02	114.2	11.9	0.28	1.0	
86	$Me_2C{=}CMe_2$	CPC 5.67	82.7	9.0	0.11	2.0	
9413-12	$Me_2C{=}CMe_2$	POEP 5.50	79.6	17.3	2.0	2.0	
9216-104	Tetralin	POEP 5.51	76.4	2.1	0.70	0.8	
9413-24	Butadiene	POEP 5.0	101.3	9.2	0.90	0.82	
9216-71	Cumene	BHD 5.61	74.6	1.1		0.10	
9413-26[d]	Cumene	NLS 5.52	74.9	5.4	0.1	0.65	

[a-c] Same significance as in Table IV. [d] pH of aqueous phase initially adjusted at ~9.

TABLE III

OXIDATION OF HYDROCARBONS IN EMULSION AND BULK AT 50°

Hydrocarbon	Emulsifying agent: CPC Concn[a]	CPC R_0[b]	POEP Concn[a]	POEP R_0[b]	$k_p/(2k_t)^{1/2}$ bulk[c]	Efficiency of radical capture[d]
α-Methylstyrene	5.6	0.36	5.5	1.2	0.196 (2.2)	0.04
Styrene	5.6	0.40	5.5	1.0	0.088 (1.0)	0.15
$Me_2C{=}CMe_2$	5.7	0.11	5.5	2.0	0.067 (0.7)	0.87
Cyclohexene			5.9	0.65	0.027 (0.3)	0.49
Cyclopentene			6.0	0.28	0.035 (0.4)	0.07
Tetralin			5.5	0.70	0.033 (0.4)	0.43
Butadiene			5.0	0.90	0.093 (1.1)	0.11

[a] Grams of emulsifier/liter of H_2O. [b] 10^4 mol of O_2 per mol of RH per min. [c] $(M \text{ min})^{-1/2}$, from D. G. Hendry, *Advan. Chem. Ser.*, 75, 24 (1968); F. R. Mayo, M. G. Syz, T. Mill, and J. K. Castleman, *ibid.*, 75, 38 (1968); D. E. Van Sickle, F. R. Mayo, R. M. Arluck, M. G. Syz, and E. S. Gould, *J. Amer. Chem. Soc.*, 89, 967, 977 (1967). [d] For POEP runs; see text for calculation.

For the single substrate, styrene, the data of Table I show that the radiation-induced oxidation rate is slightly dependent on emulsifier type. At the most commonly used concentration of emulsifying agent, 5.5 g/l., only *N*,*N*-bis(2-hydroxyethyl)dodecanamide (BHD) seems to give a slight rate enhancement (expt 9056-79). Cetylpyridinium chloride (CPC) emulsifying agent (expt 9056-15) apparently produces a 60% retardation[28] in rate compared to the average, and sodium lauryl sulfate (NLS) seems to be mildly rate retarding (expt 9056-105). There does not seem to be any clear rate distinction between anionic, cationic, and nonionic emulsifiers. Part of the effect of emulsifying agent may be that of a transfer agent that provides a more rapid termination reaction in the substrate droplet than would occur with pure hydrocarbon.

Data are less complete for substrates other than styrene, but the general effect of emulsifier type seems to be maintained (Table II). α-Methylstyrene demonstrates the most significant dependence of oxidation rate on emulsifier type. With CPC emulsifier[28] (expt 9056-94), the rate is one-sixth to one-seventh of that observed with BHD emulsifier (expt 9056-82); the rate with POEP is intermediate. With α-methylstyrene as substrate, the transfer effect mentioned above could be expected to effect a significant rate change, since the termination constant for termination between the peroxy radical from the emulsifying agent and the α-methylstyrene polyperoxy radical is expected to be 10 to 100 times as fast as the usual termination for pure α-methylstyrene.[29]

The fundamental rate difference[17] between emulsion polymerization and emulsion oxidation of styrene was confirmed (expt 9056-53, Table I). Our results show that R_p/R_0 is 100 instead of 1000; the latter result was obtained with persulfate initiator. In bulk[18] at constant R_i, $R_p/R_0 = 1.7$. Interception of the polymerization with oxygen at any stage of conversion (at least to 50%) brought about the abrupt rate diminution, although the subsequent rate was subject to an enhancement due to the polymer latex present.[25] As far as could be determined, the interception of polymerization was complete with 1 atm of oxygen over the emulsion and the subsequent oxidation rate was unchanged by raising the pressure as high as 6 atm.

Effect of Emulsifier and Substrate Concentration.— Data that indicate the effect of emulsifier and substrate concentration on the rate of oxidation of styrene and α-methylstyrene are gathered in Table IV. In-

(28) Quaternized pyridine derivatives may show unusual reactivity with peroxy radicals, hydroperoxides, or at least hydrogen peroxide: D. W. Bristol and D. C. Dittmer, *J. Org. Chem.*, 35, 2487 (1970).

(29) K. U. Ingold, *Accounts Chem. Res.*, 2, 1 (1969).

TABLE IV
EFFECTS OF EMULSIFIER AND SUBSTRATE CONCENTRATION, TEMPERATURE, AND DOSE RATE ON STYRENE AND α-METHYLSTYRENE EMULSION OXIDATION[a]

POEP concn, g/l. in aqueous phase	Substrate concn, mol/l. of H_2O	$R_0^b \times 10^4$, initial	$[\Delta O_2]$, mol/l. of H_2O	$R_0^b \times 10^4$, final	Efficiency of radical capture[c]
		Styrene			
62.3		3.5	0.050	3.8	1.6
27.8		1.7	0.75	1.7	0.37
27.2		1.7	0.049	1.4	0.37
11.5	0.97	1.4	0.18	1.5	0.25
5.53		1.0	0.051	0.2[d]	0.13
2.77		0.6	0.11	0.72	0.046
6.20	2.16	0.84			0.20
		(1.82)			
5.95	1.52	0.91			0.18
		(1.38)			
5.67	0.962	1.10			0.16
		(1.06)			
5.26	0.455	2.3			0.30
		(1.05)			
5.09	0.221	3.4			0.30
		(0.75)			
5.00	0.044	11.0			0.27
		(0.48)			
5.53 (60°)		1.3	0.16	1.5	
5.53 (30°)		0.59			
5.52 (18°)		0.28			
5.5 (1°)		0.09			
5.53[e]	0.97	0.63	0.10	0.92	
5.53[f]		0.45			
27.8[e]		1.3_8	0.14	1.4	
27.8[f]		0.7_8			
		α-Methylstyrene			
5.5[e]	0.885	0.65	0.10	0.92	
5.5[f]	0.889	0.42	0.070	0.7	
5.5	0.855	1.2			0.04
		(1.03)			
5.09	0.197	3.6			0.07
		(0.71)			
		Blank Run			
5.00		(0.18)			

[a] Emulsifying agent is poly(oxyethylene) palmitate in all runs, dose rate is 200 rads/min, and temperature is 50° unless otherwise noted. [b] Rate of oxidation in mol of O_2 per mol of substrate per min; rates in parentheses are in mol of O_2 per l. of H_2O per min. [c] See text for calculation. [d] Thermal rate. [e] Dose rate: 79 rads/min. [f] Dose rate: 43 rads/min.

creasing emulsifier concentration increases oxidation rate and, for the styrene–POEP system, a plot of log $[R_0]$ *vs.* log [POEP] (as weight per cent in the aqueous phase) gives a straight line with some scatter at the higher POEP concentrations. The slope of the line is very nearly $^1/_2$. The expected order of emulsion polymerization rates with respect to emulsifier concentration is $^3/_5$ according to the Smith–Ewart theory.[4] However, in view of the one-half-order dependence of oxidation rate on initiation rate, *i.e.*, dose rate, we do not take this emulsifier order to indicate that the emulsion polymerization rate laws apply. The total effect of increased emulsifier concentration is expected to arise from several factors, including finer division of the substrate, altered composition of the substrate (changing the feed composition of a cooxidation), and more solubilization[5] of the substrate. The first and second effects are expected to be rate enhancing and the third retarding.

In Table IV data for the oxidation of styrene and α-methylstyrene at various concentrations show that the specific rate [mol of O_2 (mol of RH)$^{-1}$ min^{-1})] increases as the amount of styrene is decreased. Part of the increase is due to the reaction of emulsifying agent, as can be seen by comparing the rate [mol of O_2 (l. of H_2O)$^{-1}$ min^{-1}], where the styrene was 0.044 *M*, with the rate where there was no styrene. Here approximately one-third of the oxygen consumption is due to emulsifying agent. At higher styrene concentrations the contribution is much less. The efficiency at which radiation results in initiation has been calculated as before and listed in the last column on Table IV. Except for the highest and lowest POEP concentrations, efficiencies are in the same range as previously found.

Effect of Dose Rate on Oxidation Rate.—The results of several emulsion oxidations done at different radiation dose rates are shown in Table IV. A plot of log rate *vs.* log dose rate shows that, for styrene at each emulsifier concentration, the order of the reaction with respect to dose rate is 0.5. The numbers actually observed are 0.45 (27.8 g of POEP/l.) and 0.50 (5.53 g of POEP/l.), which are assumed to be identical within experimental error. The one-half-order dependence indicates that exchange of radicals between the droplets and the aqueous phase is rapid at either emulsifier concentration and that bimolecular termination re-

TABLE V

EMULSION OXIDATION PRODUCTS[a]

Expt no.	Substrate	Emulsifying agent, g/l. of H_2O	Conversion, %	Time, min	Products	Yield,[b] %
9056-139	Styrene	POPE 11.5	11.9	4000	Polyperoxide[c]	81
9216-65	α-Methylstyrene	POEP 5.5	16.4	1070	Polyperoxide[d]	65
					Acetophenone	22
9216-104	Tetralin	POEP 5.5	3.1	486	Hydroperoxide[e]	93
9216-100	Tetralin	POEP 5.5	13.7	2490	Hydroperoxide[e]	58
9216-116	Tetralin[f]	None	2.7	885	Hydroperoxide[e]	91
			10.6	2440	Hydroperoxide[e]	85
			14.5	3950	Hydroperoxide[e]	89
9056-86	Tetramethyl-ethylene	CPC 5.6	10.9	1360	Hydroperoxide[g]	42
9056-56	Cyclopentene	POEP 5.5	11.2	1360	Hydroperoxide[h]	92
9216-140	Acetaldehyde[i]	None	12.8	1250	Acid[i]	98
					Peracid[e]	2
9216-148	Acetaldehyde[i,j]	None	29.0	1120	Acid[i]	95
9413-26	Cumene[k]	NLS 5.5	7.2	1440	Hydroperoxide[k]	3

[a] At 50°, dose rate 200 rads/min. Emulsion of 10 ml of substrate and 90 ml of H_2O except as noted; oxygen pressure ~4 atm. [b] Yield based on moles of substrate consumed (≅oxygen consumed). [c] Mol wt 3500; analyzed $C_{8.0}H_{8.3}O_{1.9}$. [d] Mol wt 5500; analyzed $C_{9.0}H_{10.2}O_{2.0}$. [e] Determined by titration, tetralin hydroperoxide. [f] Pure tetralin, initiation by 0.025 *M* ABN at 45°. [g] Mixture of 1-hydroperoxy-2,3-dimethyl-2-butene and 3-hydroperoxy-2,3-dimethyl-1-butene; other products detected were 14% residue, 4.5% acetone, and 2.2% tetramethylethylene epoxide. [h] Cyclopentene 3-hydroperoxide. [i] 1.0 *M* dissolved in water, acid product is acetic acid, peracid product is peracetic acid. [j] Initiation by 0.1 *M* $K_2S_2O_8$. [k] Basic emulsion, initial pH ~9; titrated product cumene hydroperoxide.

sults. This is in contrast to emulsion polymerization phenomena where, by the Smith–Ewart theory, the number of particles forming (and thus the rate) in the initial stages of the reaction is proportional to the two-fifths power of aqueous phase initiation.[4] In the latter stages of polymerization, the dependence on dose rate theoretically drops to zero, although in practice some initiation is required to maintain the polymerization rate.[30] According to the review of Stannett, *et al.*,[22] the two-fifths order expected in polymerization rate is not easily confirmed experimentally, and numbers ranging from 0.22 to 0.5 have been reported. For oxidation of methyl oleate, a substrate that reacts by an abstraction mechanism, Hyde and Verdin[7] report a reaction order of 0.5 with respect to dose rate. It is interesting that, in emulsion oxidation of styrene, the initiation rate order is close to the ideal bulk value of 0.5, while in bulk, a mechanistic anomaly causes the experimental order to be 0.6.[31]

The dose rate dependence of α-methylstyrene emulsion oxidation is significantly higher than 0.5. The usual log–log plot of the data gives a straight line of slope 0.63. A dependence of 0.5 is observed in the bulk phase. This change may be due to the transfer with POEP emulsifying agent, as described in an earlier section. Kinetic analyses[32] of fully inhibited systems show first-power dependence on initiation rate.

Where initation was by potassium persulfate (expt 9056-139 of Table I), the apparent order with respect to persulfate concentration is 0.56. Complication[33] in the decomposition kinetics of potassium persulfate obscures the significance of this result. That the decomposition of potassium persulfate in aqueous solution is strongly influenced by minor changes in the medium is illustrated by comparison of oxidation rates of expts 9056-130, -110, -133, and -136 and 9416-18 of Table I. Addition of sodium lauryl sulfate to POEP-emulsified styrene in potassium persulfate solution increased the rate of oxidation from 2.6 to 7.0 × 10^{-4} mol (mol^{-1} min^{-1}). Addition of sodium lauryl sulfate to radiation-induced emulsion oxidations did not affect the rate.

Effect of Temperature on Emulsion Oxidation Rate.—Data for experiments at different temperatures in Table IV were used for preparing an Arrhenius plot to determine the overall activation energy of the emulsion oxidation process. The points seem to define two lines, one from 30 to 60° of slope, corresponding to an activation energy of 5.6 kcal/mol, and another from 1 to 30°, indicating an activation energy of 10.6 kcal/mol. However, the statistical line for all the points yields an activation energy of 8.6 kcal/mol, which corresponds precisely with the reported value for bulk styrene oxidation.[34] The energy of activation for the production of radicals from the radiolysis of water is assumed to be zero. The energy of activation for radiation-initiated emulsion polymerization of styrene was recently found[22] to be 3.6 kcal/mol, in agreement with the pioneering work of Ballantine,[21] although in bulk a value of 8.2 kcal/mol is found.[35]

Products from Oxidation of Emulsions.—The products reported for the oxidations of the emulsions in Table V are qualitatively consistent with the results obtained for the corresponding oxidations in the bulk. The 81% yield of styrene polyperoxide is comparable to the 95% yield for the bulk reaction,[18] while the 65% yield of poly-α-methylstyrene peroxide compares with an expected value of 81%.[36] The lower yields may arise from a lower effective concentration of oxygen in the emulsion system than in the bulk. In each case the yields correspond with the results in bulk expected near 1 atm of oxygen, or slightly lower, rather than 4 atm, at which the emulsion reactions were run. However,

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(31) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **43**, 2729 (1965); **44**, 1113 (1966).

(32) Reference 16, p 430.

(33) C. E. M. Morris and A. G. Parts, *Makromol. Chem.*, **119**, 212 (1968).

(34) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **43**, 2729 (1965).

(35) Reference 16, p 84.

(36) F. R. Mayo and A. A. Miller, *J. Amer. Chem. Soc.*, **80**, 2480 (1958).

the lower yields may also reflect the increased difficulty in isolating products from emulsions, or in part of the oxygen being present as oxidized emulsifier. The molecular weights of these polyperoxides from emulsion oxidations are comparable to bulk oxidation products.

The comparison of yield of tetralin hydroperoxide in emulsion and in bulk oxidation (initiated by azobisisobutyronitrile) indicates that the yield drops off with conversion faster in emulsion. Hyde and Verdin[7] observed the same phenomenon with methyl oleate. The hydroperoxide yields in the emulsion oxidation of tetramethylethylene and cyclopentene are nearly identical with those observed in the bulk.[23,24] In the case of tetramethylethylene, the analysis for acetone is complicated by the high solubility of acetone in the aqueous phase. While the conversion of cumene to cumene hydroperoxide is reportedly favorable in thermally initiated basic emulsions,[37] our radiation result gave a very low hydroperoxide yield.

Registry No.—Cobalt-60, 10198-40-0; α-methylstyrene, 98-83-9; cyclohexene, 110-83-8; cyclopentene, 142-29-0; tetramethylethylene, 563-79-1; tetralin, 119-64-2; butadiene, 106-99-0; cumene, 98-82-8; styrene, 100-42-5.

(37) G. P. Armstrong, R. H. Hall, and D. C. Quin, *J. Chem. Soc.*, 666 (1950).

The Chemistry of Carbanions. XX. A Comparison of α-Chloro Enolate Anions and α-Diazo Ketones[1a]

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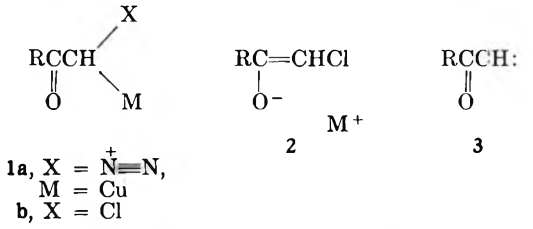
The α-chloro ketones, 2-chlorocyclohexanone (**5**), chloromethyl cyclohexyl ketone (**7**), and phenacyl chloride (**13**), have been converted to the corresponding enol acetates and trimethylsilyl enol ethers. These enol derivatives have served as precursors for the corresponding lithium α-chloro enolates **6**, **8**, and **16** which are stable intermediates. Even the addition of copper(I) compounds or the formation of α-mercuri derivatives of these enolates does not promote their decomposition to α-ketocarbenes. In contrast, the α-diazo derivatives **17** and **21** of acetophenone and methyl cyclohexyl ketone are readily decomposed by added copper(I) derivatives. The soluble complex, $(n\text{-Bu}_2\text{S})_2\text{CuI}$, is an especially convenient catalyst for the decomposition of these α-diazo ketones, compound **21** being rapidly decomposed in solution at 5–10°. With small amounts of this catalyst and excess olefin the norcarane derivative **22** was the major product. With an equimolar amount of this catalyst, the keto sulfide **26** (believed to arise from a sulfur ylide intermediate) became the major monomeric product.

To pursue further the idea[2] that the copper-catalyzed reactions of α-diazo carbonyl compounds may involve copper(I) derivatives such as structure **1a** which pos-



1a, X = $\overset{+}{\text{N}}\equiv\text{N}$, M = Cu
b, X = Cl

2 **3**

sess a good leaving group ($\text{N}^+\equiv\text{N}$) at the α position, we have investigated the behavior of certain metal derivatives of α-chloro enolate ions (**2**). We wished to learn whether certain of these materials (*e.g.*, **1b** or **2**) would show either behavior similar to the copper(I)–diazo ketone reagent or the behavior expected of an α-keto carbene **3**. The metal enolates of α-halo esters and α-halo ketones have served as intermediates in a number of synthetically useful reactions such as the Darzens glycidic ester condensation and related reactions,[3,4] the formation of cyclopropane derivatives by Michael additions involving α-chloro enolates,[5] and the reaction of α-bromo enolates with trialkylboranes.[6] In all of these cases, it is probable that the metal α-halo enolates (*e.g.*, **2**) and not the α-keto carbenes **3**, which might be formed from the enolates, are the actual reactants. Further evidence in support of the view that α-halo enolate anions (*e.g.*, **2**) are not rapidly converted to α-keto carbenes **3** has been obtained by the formation and subsequent acylation of several α-halo enolates to form α-halo enol esters[7–9] such as **4**. In the present study we have generated several metal α-chloro enolate anions **2** from either enol acetate[10] or trimethylsilyl enol ether[11,12] precursors.

Preparation of Lithium α-Chloro Enolates.—The most successful of previous preparations[7–9] of α-chloroenol esters have involved acylation of the inter-

(1) (a) This research has been supported by Research Grant No. AFOSR-68-1518, from the Directorate of Chemical Sciences, Air Force Office of Scientific Research, and by Public Health Service Grant No. 1-RO1-CA10933 from the National Cancer Institute. (b) Department of Chemistry, Georgia Institute of Technology, Atlanta, Ga. (c) National Institutes of Health Predoctoral Fellow, 1966–1969. (d) National Institutes of Health Predoctoral Fellow, 1968–1970.

(2) (a) H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 47, 53 (1968), and references cited therein; (b) W. R. Moser, *J. Amer. Chem. Soc.*, **91**, 1135, 1141 (1969), and references cited therein: (c) V. Dave and E. W. Warnhoff, *Org. React.*, **18**, 217 (1970).

(3) M. S. Newman and B. J. Magerlein, *ibid.*, **5**, 413 (1949).

(4) M. Ballester, *Chem. Rev.*, **55**, 283 (1955).

(5) L. L. McCoy, *J. Org. Chem.*, **25**, 2078 (1960); **29**, 240 (1964); *J. Amer. Chem. Soc.*, **84**, 2246 (1962).

(6) H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *ibid.*, **90**, 818, 1911 (1968); **91**, 2150 (1969), and subsequent publications.

(7) R. E. Lyle and R. A. Covey, *ibid.*, **75**, 4973 (1953).

(8) K. G. Rutherford and C. L. Stevens, *ibid.*, **77**, 3278 (1955).

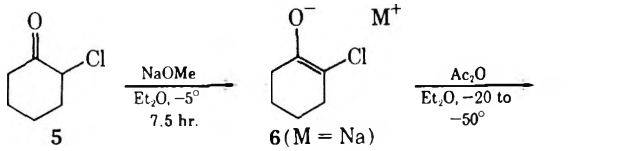
(9) (a) D. J. Cooper and L. N. Owen, *J. Chem. Soc. C*, 533 (1966); (b) L. N. Owen and R. Sridhar, *ibid.*, 564 (1970).

(10) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965); (b) H. O. House, *Rec. Chem. Progr.*, **28**, 99 (1967).

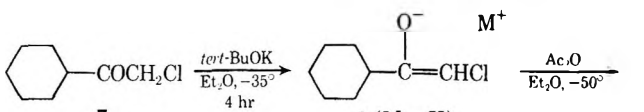
(11) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968).

(12) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

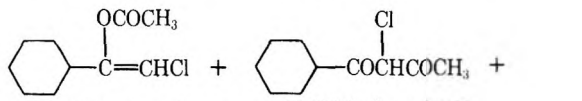
mediate α-chloro enolates formed by reaction of the chloro ketone with a suspension of sodium methoxide in ether at −20 to −50°.[8,9a] This procedure takes advantage of the fact that in unsymmetrical ketones such as **5** or **7** the C–H bond adjacent to both the carbonyl group and the chlorine atom is significantly more acidic (about 2 pK_a units)[13] than C–H bonds adjacent only to a carbonyl group. Although we have successfully adapted this procedure to the formation of the α-chloroenol acetates **4** and **9** (eq A and B),



5 **6** (M = Na) **4** (67% yield) (A)

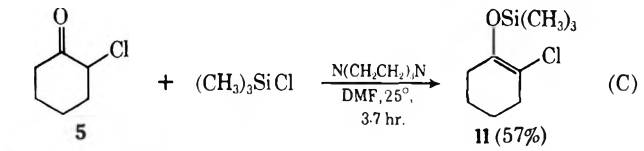


7 **8** (M = K)

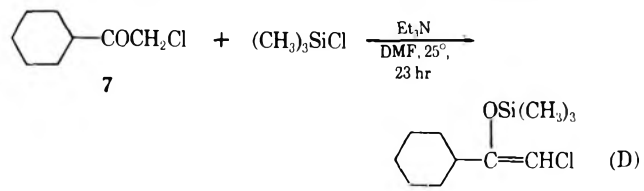


9 (65% of product) **10** (18% of product) other products (B)

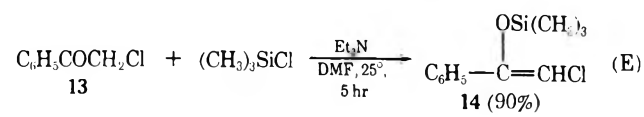
a far more useful synthetic procedure involves the formation of the corresponding trimethylsilyl enol ethers. The procedures, illustrated in eq C, D, and E,



5 **11** (57%) (C)

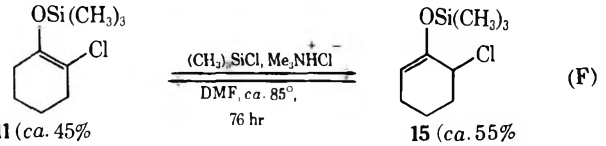


7 **12** (32%) (D)



13 **14** (90%) (E)

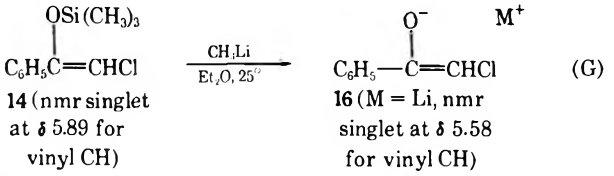
are based on a previously described method[12] and probably also owe their success to the relatively high acidity of the C–H bond adjacent to both the chlorine atom and the carbonyl group. It seems likely that the enol ethers **11** and **12** are formed in kinetically controlled processes since subjection of the enol ether **11** to conditions (eq F) known[12] to equilibrate silyl enol ethers



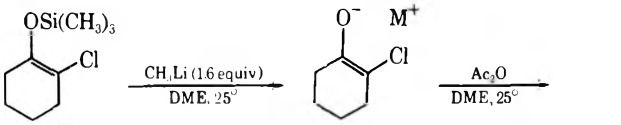
11 (*ca.* 45% of mixture) **15** (*ca.* 55% of mixture) (F)

produced a second substance believed to be the enol ether **15**.

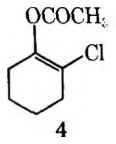
With samples of the enol derivatives **4**, **9**, **11**, **12**, and **14** available, we prepared the corresponding lithium α-chloroenolates **6**, **8**, and **16** and studied their thermal stabilities. As indicated in eq H–K, the



14 (nmr singlet at δ 5.89 for vinyl CH) **16** (M = Li, nmr singlet at δ 5.58 for vinyl CH) (G)

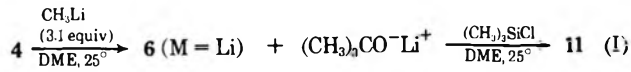


11 **6** (M = Li)



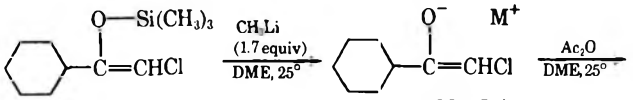
4 (H)

Time before Ac_2O added, hr	Yield of 4, %
1	90
24	87

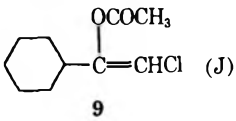


4 **6** (M = Li) + $(CH_3)_3CO^-Li^+$ **11** (I)

Time before $(CH_3)_3SiCl$ added, hr	Yield of 11, %
1	83
24	88

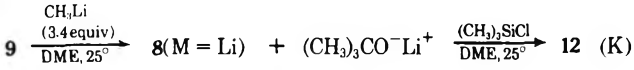


12 (N) **8** (M = Li)



9 (J)

Time before Ac_2O added, hr	Yield of 9, %
1	81
24	75



9 **8** (M = Li) + $(CH_3)_3CO^-Li^+$ **12** (K)

Time before $(CH_3)_3SiCl$ added, hr	Yield of 11, %
1.0	92
8.0	82

lithium enolates **6** and **8** are very stable and could be recovered as appropriate derivatives in high yield after 24 hr. As a result of these observations it is

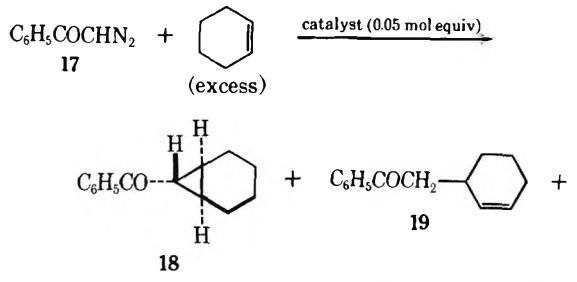
(13) (a) R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953). (b) R. P. Bell, G. R. Hillier, J. W. Mansfield, and D. G. Street, *J. Chem. Soc. B*, 827 (1967). (c) In a chloro ketone analogous to **7**, the base-catalyzed exchange

$$RCOCH_2Cl + MeOD \overset{NaOMe}{\rightleftharpoons} RCOCHDCl + MeOH$$

is faster than other possible reactions which may occur: H. O. House and F. A. Richey, Jr., *J. Org. Chem.*, **32**, 2151 (1967).

clear that the lithium α-chloroenolates (2, M = Li) do not undergo a ready thermal elimination of lithium chloride to form α-keto carbenes **3**.

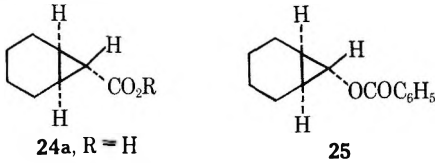
Comparison of α-Diazo Ketones and α-Chloro Enolates.—Before examining the effect of added copper(I) salts on the stability of the α-chloro enolates **2**, we examined the copper-catalyzed decomposition of the related diazo ketones **17** and **21**. The results obtained with the diazo ketone **17** and various copper compounds are summarized in eq L. The stereochemistry of the



$C_6H_5COCH{=}CHCOC_6H_5$ (L)
20

Catalyst	Reaction time, min	Temp, °C	Product yields, % 18	19	20
$(MeO)_3PCuI$ (homogeneous)	60	25	11–27	1–3	1–3
$(PhO)_3PCuI$ (homogeneous)	90	25	31–33	3–7	5–7
$(Bu_2S)_2CuI$ (homogeneous)	60	25	37–40	2–3	4–5
C_6F_5Cu (homogeneous)	10–15	25	24–32	3–5	3–4
CuI (heterogeneous)	15–20	80	55–57	4	7–8
CuO (heterogeneous)	20–25	80	51–53	3–4	5–7

cyclopropyl ketone **18** was established by a Baeyer–Villiger oxidation and subsequent hydrolysis to form the known acid **24a**.

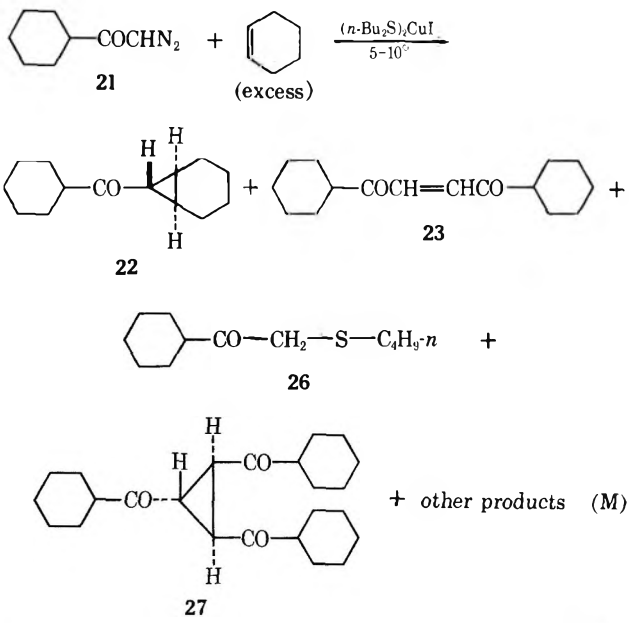


24a, R = H
b, R = C_6H_5
c, R = C_2H_5

25

These results agree with earlier observations, made with α-diazo esters,[2] that reactions involving a catalyst which is initially in solution proceed readily at room temperature. Whether the actual catalyst remains in solution at 25° is less clear, since all of these reaction mixtures became very dark in color as soon as decomposition of the diazo ketone began. Of interest was the fact that the yield of the cyclopropyl ketone **18**, the usual synthetic objective in these decompositions, was consistently higher when one of the insoluble catalysts was employed. The same observation was made in our earlier study of diazo ester reactions.[2a]

The results obtained on decomposition of the diazo ketone **21** in cyclohexene with $(n\text{-BuS})_2CuI$ as a catalyst are summarized in eq M. With small amounts (1–5 mol %) of this soluble catalyst the major volatile products were the norcarane **22** and the enedione **23**; although it is likely that a small amount of the triketone **27** was also formed in these reactions, we were not able to obtain quantitative data because the tri-



Reactant concn, M 21	$(n\text{-Bu}_2S)_2CuI$	Product yields, % 22	23	26
0.36[a]	0.0088	33	32	
0.065	0.0012	56	11	
0.34[a]	0.34	13	5	22

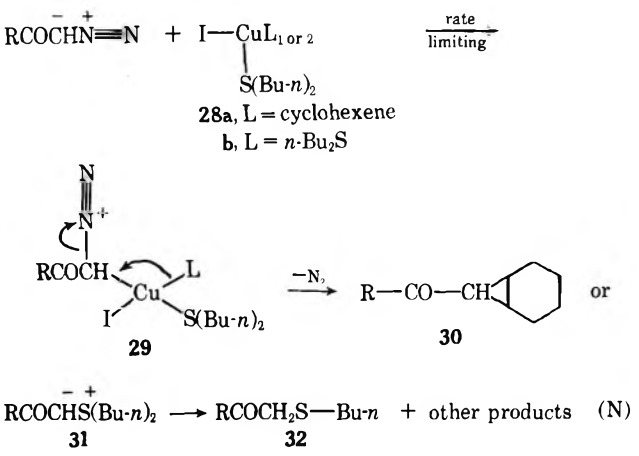
[a] The solvent contained 10% (by volume) of 1,2-dimethoxyethane.

ketone **27** was not eluted from the glpc columns used for analysis. As might be expected, the proportion of norcarane **22** to dimer **23** was increased when dilute solutions of the diazo ketone were employed. A similar concentration effect may be responsible for the improved yields of norcarane **18** obtained when the diazo **17** was decomposed with heterogeneous catalysts. The stereochemistry of the predominant norcarane isomer is believed to be that indicated in structure **22** by analogy with the stereochemistry of the benzoyl analog **18**.

When a full equivalent of the catalyst $(n\text{-Bu}_2S)_2$-CuI was used to decompose a solution of the diazo ketone **21** in cyclohexene (see eq M), the major volatile product became the keto sulfide **26** and the yields of **22** and **23** were lowered. From a preparative reaction in cyclohexane solution with 100 mol % of the soluble copper complex, the major products isolated by column chromatography were the keto sulfide **26** and the triketone **27** along with a tetramer (see Experimental Section). The structures of these products were confirmed by their physical and spectral properties, particularly the nmr spectra of the materials in which the hydrogen atoms near the carbonyl function were shifted by added europium(III) tri(dipivalolylmethide).[14] The decomposition of the diazo ketone **21** in the presence of $(n\text{-Bu}_2S)_2CuI$ occurred relatively rapidly in the temperature range 5–10°. In this temperature range the reaction mixture remained homogeneous even when 100 mol % of the copper complex was present. Consequently, we were able to follow the course of this reaction by observing the nmr spectrum of a pentane solution containing equimolar amounts of the diazo ketone and $(n\text{-Bu}_2S)CuI$. *From these observations we can conclude unambiguously that no appreciable concentration of a diazo ketone–copper(I)*

(14) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971), and references cited therein.

complex such as **1a** *accumulates in the reaction solution as the decomposition proceeds.* From these various observations we believe that the copper(I)-catalyzed diazo ketone reactions are best interpreted as shown in eq N. When low concentrations of a copper(I) complex such as **28** are present, we would expect an



$$RCOCHS(Bu\text{-}n)_2 \longrightarrow RCOCH_2S\text{—}Bu\text{-}n + \text{other products} \quad (N)$$

31 **32**

appreciable amount of the complex to be present in solution as a structure such as **28a** with one (or two) olefin molecules as donor ligands. At higher catalyst concentrations, more of the complex should be present as **28b** with two (or three) thioether molecules as donor ligands. Following a rate-limiting coordination of the copper(I) complex **28** with diazo ketone, the resulting diazonium salt **29** undergoes rapid loss of nitrogen and transfer of a donor ligand L from copper to carbon to form either a norcarane **30** or a sulfur ylide **31**.[15,16] Although a sulfur ylide **31** appears to be the most likely precursor of the keto sulfide **32** (by proton transfer and elimination of 1-butene), our data do not allow us to decide whether the known[17] copper-catalyzed decomposition of a sulfur ylide **31** is an important route to the dimeric (*e.g.*, **20** and **23**) and trimeric (*e.g.*, **27**) products. However, it is clear (eq L) that at least dimeric products may arise by reaction paths which do not involve sulfur ylide intermediates.

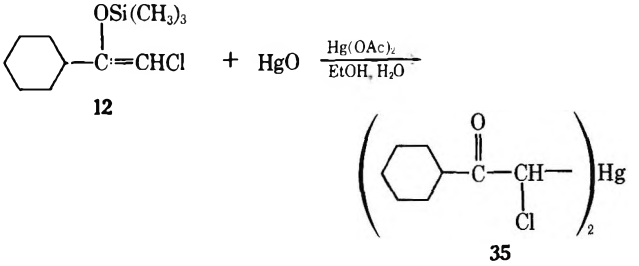
With this information as a background we then examined the behavior of solutions containing equimolar amounts of $(n\text{-}Bu_2S)_2CuI$ and each of the lithium α-chloro enolates **8** and **16**. In ether solution at $-16°$, the nmr spectrum of the lithium enolate **16** was essentially unchanged by the addition of an equimolar amount of the copper(I) complex.[18] When this solution was refluxed for 6 hr and then hydrolyzed, the predominant volatile product was the α-chloro ketone **13**; no 1,2-dibenzoylethylene (**20**) was detected in the reaction product. Solutions of the lithium enolate **8** and either 5 or 100 mol % of $(n\text{-}Bu_2S)_2CuI$ were allowed to decompose in the same mixture of cyclohexene and 1,2-dimethoxyethane used in studies with the diazo ketone **21**. Although these solutions clearly underwent reaction, as indicated by the separation of a black solid (presumably metallic copper), the only volatile product formed in appreciable amount (72–100% yield) was the chloro ketone **7**. None of the products **22**, **23**, or **26** was detected, indicating that the α-chloro enolate **8** does not react with copper(I) complexes in the same manner (see structure **29**) as α-diazo ketones. These results suggest that the chloro enolates **2** do not form covalent compounds (*e.g.*, **1b**) with the added copper(I) complex. We suggest that the decomposition reaction observed is an electron transfer from the enolate to the copper(I) species to produce metallic copper and a radical of the type $RCO\dot{C}HCl$, which abstracts hydrogen from the solvent to form the observed chloro ketone product **7**. The same type of reaction is apparently involved in the subsequently described thermal decomposition of the α-chloro-α-mercuric ketone **35**.

In an effort to produce a substance that has a metal bound to the α carbon of an α-chloro ketone, we examined the reaction of the silyl enol ethers **12** and **14** with HgO. In other studies[19] we have found that use of this reaction with nonhalogenated silyl enol ethers (*e.g.*, **33**) yields the corresponding α-mercuric ketones **34** with nmr absorption, which clearly establishes the

$$RC(OSi(CH_3)_3)=CH_2 + HgO \xrightarrow[EtOH,\ H_2O]{Hg(OAc)_2} (RCCH_2-)_2Hg \quad (O)$$

33 **34**

presence of C–Hg bond. Application of this reaction to the chlorinated silyl enol ethers **12** and **14** produced high-melting, insoluble materials which were very difficult to purify and characterize. We succeeded in obtaining a sample of one product which had a composition and infrared absorption consistent with structure **35**. However, the insolubility of this product



prevented us from obtaining satisfactory nmr data to establish the presence of a C–Hg bond from the magnitude of the coupling constant, $J_{H-^{199}Hg}$.

When the product **35** was decomposed at 230°, the chloro ketone **7** was found to distil from the decomposed material. A suspension of **35** in refluxing cyclohexene appeared to undergo no change and after hydrolysis with aqueous acid the chloro ketone **7** was recovered but no norcarane **22** was detected. Although the α-mercuric dichloro ester **36** has been found to decompose slowly (forming products apparently derived from $Cl\dot{C}CO_2CH_3$) in refluxing chlorobenzene (132°),[20] our finding that the related mono-

(15) For other examples of sulfur ylide formation, see (a) W. Ando, K. Nakayama, K. Ichibori, and T. Migita, *ibid.*, **91**, 5164 (1969); (b) W. Ando, T. Yagihara, S. Tozune, S. Nakaido, and T. Migita, *Tetrahedron Lett.*, 1979 (1969); (c) F. Dost and J. Gosselck, *ibid.*, 5091 (1970); (d) F. Serratosa and J. Quintana, *ibid.*, 2245 (1967).

(16) For examples where donor ligands appear to have been transferred from copper(I) to the α carbon of an α-diazo ketone, see ref 15c and (a) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and T. Shimizu, *J. Org. Chem.*, **33**, 544 (1968); (b) T. Sato and S. Watanabe, *Chem. Commun.*, 515 (1969).

(17) B. M. Trost, *J. Amer. Chem. Soc.*, **89**, 138 (1967).

(18) We have noted previously that the addition of soluble copper(I) compounds seems to have no effect on the rate at which lithium enolates undergo Michael reactions or reaction with alkyl halides: H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3615 (1969).

(19) H. O. House, M. Gall, H. D. Olmstead, and N. Peet, unpublished work.

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chloro derivative **35** is stable is in agreement with the general experience that the ease of thermal decomposition of chloroalkyl mercurials lies in the order $RHgCCl_3 > RHgCCl_2R > RHgCClR_2$.[20b]

$C_6H_5HgCCl_2CO_2CH_3$
36

Experimental Section[21]

Starting Material and Reagents.—Commercial samples of 2-chlorocyclohexanone, ω-chloroacetophenone, and halide-free ethereal solutions of methyllithium were employed. The methyllithium solutions were standardized by the titration procedure of Watson and Eastham.[22] Diazomethane was prepared from bis(*N*-methyl-*N*-nitroso)terephthalamide.[23] 1,2-Dimethoxyethane was distilled from $LiAlH_4$ immediately before use. Freshly distilled samples of commercial trimethylsilyl chloride were treated with small amounts of Et_3N and then filtered under anhydrous conditions (to separate any $Et_3NH^+Cl^-$ present) before being used in reactions with solutions of lithium enolates.

Reaction of cyclohexanecarboxylic acid with excess $SOCl_2$ in CH_2Cl_2 yielded the acid chloride, bp 44–45° (5 mm) [lit.[24] bp 184–188° (755 mm)], which was converted to the chloro ketone **7** by reaction with cold (0°), ethereal diazomethane as previously described.[25] The chloro ketone **7** was collected in 74% yield as a colorless liquid, bp 75–85° (3.1 mm), $n^{25}D$ 1.4762–1.4775 [lit. mp 1–2.5°,[15] bp 114–115° (20 mm),[26] $n^{25}D$ 1.4773[26]], which contained [glpc analysis, 1,2,3-tris-(β-cyanoethoxy)propane on Chromosorb P] the chloro ketone **7** accompanied by small amounts of low-boiling impurities. A pure sample of the chloro ketone **7** was collected (glpc): ir (CCl_4) 1740 and 1712 cm^{-1} (C=O); nmr (CCl_4) δ 4.03 (2 H, s, $COCH_2Cl$) and 1.0–2.9 (11 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity), 162, 160 (2, M^+), 111 (25), 83 (100), 55 (44), and 41 (20).

Preparation of the Trimethylsilyl Enol Ethers. A. From ω-Chloroacetophenone (13).—A solution of 21.6 g (140 mmol) of ω-chloroacetophenone in 20 ml of Me_2NCHO was treated with a solution of 23.9 g (220 mmol) of Me_2SiCl and 38.4 g (380 mmol) of Et_3N in 80 ml of Me_2NCHO. After the initial exothermic reaction subsided, the mixture was stirred at 25° for 5 hr and then partitioned between pentane and saturated, aqueous $NaHCO_3$. The organic extract was dried, concentrated, and distilled to separate 28.6 g (90%) of the silyl enol ether **14**: bp 75–75.5° (1 mm); $n^{25}D$ 1.5214; ir (CCl_4) 1620 (shoulder) and 1615 cm^{-1} (enol C=C); nmr (CCl_4) δ 7.1–7.6 (5 H, m, aryl CH), 5.89 (1 H, s, vinyl CH),[27] and 0.20 [9 H, $(CH_3)_3Si$]; mass spectrum *m/e* (rel intensity), 228 (13) and 226 (33, M^+), 190 (24), 183 (22), 177 (22), 157 (22), 155 (58), 95 (37), 93 (100), 73 (97), and 45 (36).

Anal. Calcd for $C_{11}H_{15}ClOSi$: C, 58.23; H, 6.65. Found: C, 58.16; H, 6.65.

B. From Chloromethyl Cyclohexyl Ketone (7).—A solution of 32.6 g (300 mmol) of Me_3SiCl, 20.2 g (200 mmol) of Et_3N, and 9.5 g (59 mmol) of the chloro ketone **7** in 100 ml of Me_2NCHO was stirred for 4 hr and subjected to the previously described isolation procedure. Fractional distillation afforded early fractions, bp 80–81° (3.5 mm), containing the chloro ketone **7** and 4.40 g (32%) of the silyl ether **12**: bp 85–86° (3.5 mm); $n^{25}D$ 1.4692–1.4699; ir (CCl_4) 1627 cm^{-1} (enol C=C); nmr (CCl_4) δ 5.25 (1 H, s, vinyl CH),[27] 0.8–2.1 (11 H, m, aliphatic CH), and 0.27 [9 H, s, $(CH_3)_3Si$]; mass spectrum *m/e* (rel intensity), 234 (12) and 232 (33, M^+), 183 (24), 177 (53), 149 (26), 147 (37), 93 (39), 83 (33), 79 (28), 73 (100), 55 (25), and 41 (20).

Anal. Calcd for $C_{11}H_{21}ClOSi$: C, 56.74; H, 9.09; Cl, 15.23. Found: C, 56.70; H, 8.90; Cl, 15.39.

C. From 2-Chlorocyclohexanone (5).—The same procedure was followed with a solution of 25.2 g (250 mmol) of 1,4-diazabicyclo[2.2.2]octane, 19.98 g (184 mmol) of Me_3SiCl, and 15.37 g (116 mmol) of the chloro ketone **5** in 50 ml of Me_2NCHO. The silyl enol ether **11** was collected as 13.5 g (57%) of colorless liquid, bp 82° (4 mm), $n^{25}D$ 1.4638. A sample for analysis was collected from a glpc column (Carbowax, 20M, on Chromosorb P): ir (CCl_4) 1675 cm^{-1} (enol C=C); nmr (CCl_4) δ 1.3–2.6 (8 H, m, aliphatic CH) and 0.20 [9 H, s, $(CH_3)_3Si$]; mass spectrum *m/e* (rel intensity) 206 (16) and 204 (40, M^+), 191 (23), 189 (65), 95 (35), 93 (100), 75 (28), 73 (92), and 45 (37).

Anal. Calcd for $C_9H_{17}ClOSi$: C, 52.79; H, 8.37. Found: C, 52.81; H, 8.31.

In experiments where triethylamine rather than 1,4-diazabicyclo[2.2.2]octane was used, the conversion of the chloro ketone **5** to the silyl enol ether **11** was slower. Heating the reaction mixture resulted in the appearance of a new glpc peak (Carbowax 20M on Chromosorb P) believed to be the enol ether **15** (retention time 21.0 min) as well as peaks corresponding to the enol ether **11** (17.4 min) and the chloro ketone **5** (35.6 min). A suspension of 153 mg (1.6 mmol) of Me_3NHCl (freshly sublimed), 25.7 g (236 mmol) of Me_3SiCl, and 6.12 g (29.9 mmol) of the enol ether **11** in 60 ml of Me_2NHCO was heated to *ca.* 85° with stirring and aliquots of the reaction mixture were removed periodically and subjected to the usual isolation procedure followed by glpc analysis. After 76 hr, when equilibration appeared to be complete, the low-boiling components were distilled from the mixture and the residue was partitioned between pentane and aqueous $NaHCO_3$. The pentane solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried over $CaSO_4$, decolorized with charcoal, and concentrated. The residual pale yellow liquid (4.88 g) exhibited glpc peaks corresponding to the enol ethers **11** (*ca.* 34%) and **15** (*ca.* 44%) and to the chloro ketone **5** (*ca.* 22%). Collected samples of **11** and **5** were identified with authentic samples by comparison of ir spectra and glpc retention times. A collected sample of the silyl enol ether **15** was obtained as a colorless liquid: ir (CCl_4) 1660 cm^{-1} (enol C=C); nmr (CCl_4) δ 4.8–5.0 (1 H, m, vinyl CH), 4.2–4.4 (1 H, m, COCHCl), 1.4–2.5 (6 H, m, aliphatic CH), and 0.20 [9, H, s, $(CH_3)_3Si$]; mass spectrum *m/e* (rel intensity) 206 (11) and 204 (29, M^+), 191 (27), 189 (76), 169 (36), 95 (28), 93 (67), 79 (26), 75 (58), 73 (100), 68 (35), 55 (37), and 45 (26). Attempts to store or work with this material were complicated by its rapid conversion or mixtures containing the isomer **11** and the ketone **5**.

Anal. Calcd for $C_9H_{17}ClOSi$: C, 52.79; H, 8.37. Found: C, 53.11; H, 8.28.

Preparation of the Enol Acetates. A. From 2-Chlorocyclohexanone (5).—To a cold (−7°) suspension of 17.05 g (315 mmol) of NaOMe in 300 ml of Et_2O was added 9.33 g (70.3 mmol) of the chloro ketone **5**. After the resulting mixture had been stirred at −5° for 7.5 hr, it was cooled to −50° and 92.4 g (904 mmol) of Ac_2O was added. The reaction mixture, which initially warmed to −20°, was stirred at *ca.* −50° for 20 min and then allowed to warm to room temperature over 60 min. The resulting suspension was poured into a mixture of 200 ml of pentane and 150 ml of saturated, aqueous $NaHCO_3$, and additional solid $NaHCO_3$ was added until all the HOAc was neutralized. The organic phase was separated, washed successively with aqueous $NaHCO_3$ and H_2O, dried, and concentrated. An 8.52-g portion of the residual orange liquid (10.02 g) was distilled through a 40-cm spinning-band column to separate 5.69 g (67%) of the enol acetate **4** as a colorless liquid, bp 107–108° (24 mm), $n^{28}D$ 1.4740, which contained (glpc, Carbowax 20M on Chromosorb P) the enol acetate **4** (retention time 40.1 min) accompanied by small amounts (3–5%) of the chloro ketone **5** (33.1 min). A collected (glpc) sample of the enol acetate **4** was characterized: ir (CCl_4) 1765 (enol ester C=O) and 1685 cm^{-1} (enol C=C); nmr ($CDCl_3$) δ 1.5–2.7 (multiplet, aliphatic CH); mass spectrum *m/e* (rel intensity) 176 (3) and 174 (9, M^+), 134 (27), 132 (100), 104 (26), 97 (58), and 43 (82).

Anal. Calcd for $C_8H_{11}ClO_2$: C, 55.02; H, 6.35; Cl, 20.30. Found: C, 55.14; H, 6.53; Cl, 20.15.

(21) 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 at 60 Mc with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shift values are expressed in δ values (ppm) relative to a tetramethylsilane internal standard. The mass spectra were obtained with an Hitaehi (Perkin-Elmer) mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

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(27) Although the narrow line widths observed for the nmr peaks would suggest that this product is a single stereoisomer, we have no compelling evidence on this point.

B. From Chloromethyl Cyclohexyl Ketone (7).—A mixture of 3.90 g (35.1 mmol) of *tert*-BuOK, 1.98 g (12.3 mmol) of the chloro ketone **7**, and 60 ml of Et_2O was stirred at −35° for 4 hr and then cooled to −50° and mixed with 21.7 g (212 mmol) of Ac_2O. After the resulting solution had been stirred at −50° for 10 min it was allowed to warm to 25° over a 60-min period and then subjected to the previously described isolation procedure. The crude liquid product contained (glpc analysis, silicone gum, SE-30, on Chromosorb P) four volatile components: the chloro ketone **7**, *ca.* 11%, retention time 16.5 min; the enol acetate **9**, *ca.* 65%, 37.5 min; a product thought to be the diketone **10**, *ca.* 18%, 44.8 min;[28] and an unidentified component, *ca.* 6%, 102.6 min. Samples of each of the major components **7**, **9**, and **10** were collected (glpc) and the starting ketone was identified by comparison of glpc retention times and ir spectra. The enol acetate **9** was obtained as a colorless liquid: ir (CCl_4) 1775 (enol ester C=O) and 1650 cm^{-1} (C=C); nmr (CCl_4) δ 5.7 (1 H, partially resolved doublet, vinyl CH), 2.16 (3 H, s, CH_3CO), and 0.9–2.3 (11 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 204 (1) and 202 (3, M^+), 162 (17), 160 (51), 111 (38), 83 (36), and 43 (100).

Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41. Found: C, 59.60; H, 7.43.

The material thought to be diketone **10** has ir absorption at 1715 and 1610 (broad) cm^{-1} (enolic β diketone); mass spectrum *m/e* (rel intensity), 204 (9) and 202 (26, M^+), 121 (19), and 119 (52, $O^+{\equiv}CCHClCOCH_3$), 111 (32), 83 (100), 55 (65), 43 (48), and 41 (33).

Preparation of the Lithium Chloro Enolate 6. A. From the Silyl Ether 11.—A solution of 8.25 mmol of MeLi and several milligrams of 2,2-bipyridyl (as an indicator) in 8.0 ml of 1,2-dimethoxyethane was treated with 1.076 g (5.25 mmol) of the silyl enol ether **11** and the resulting solution was stirred at 25°. Periodically, 1-ml aliquots were removed, quenched in 2.0 ml of Ac_2O, stirred for 10 min, and then partitioned between pentane and aqueous $NaHCO_3$. The organic phase was mixed with an internal standard (tetralin) and analyzed to give the results summarized in eq H. On the glpc column (Carbowax 20M on Chromosorb P) used for analysis the retention times were: silyl ether **11**, 17.4 min; tetralin, 23.8 min; chloro ketone **5**, 34.6 min; enol acetate **4**, 42.0 min. The gas chromatography equipment was calibrated with known mixtures of authentic samples and collected (glpc) samples of each of the peaks were identified with authentic samples by comparison of glpc retention times and ir spectra.

B. From the Enol Acetate 4.—A solution prepared from 6.6 mmol of MeLi and 370 mg (2.12 mmol) of the enol acetate **4** in 6.0 ml of 1,2-dimethoxyethane was stirred at 25° and 1.0-ml aliquots were removed periodically and quenched in 2.0 ml of Me_3SiCl. The resulting mixtures were stirred for 10 min and then subjected to the previously described isolation and analysis procedures to give the results summarized in eq I.

Preparation of the Lithium Chloro Enolate 8. A. From the Silyl Ether 12.—The enolate solution, prepared from 8.25 mmol of MeLi and 1.122 g (4.83 mmol) of the silyl enol ether **12** in 6.0 ml of 1,2-dimethoxyethane, was stirred at 25° and aliquots were removed, quenched in Ac_2O, and then subjected to the previously described isolation procedure. An internal standard (pentamethylbenzene) was added to each crude product and it was analyzed to give the results indicated in eq J. On the glpc column used (silicone gum, SE-30, on Chromosorb P), the retention times were: chloro ketone **7**, 14.6 min; pentamethylbenzene, 20.7 min; enol acetate **9**, 31.6 min; silyl enol ether **12**, 34.3 min. The gas chromatography equipment was calibrated with known mixtures of authentic samples, and collected (glpc) samples of the reaction products were identified with authentic samples by comparison of glpc retention times and ir spectra.

B. From the Enol Acetate 9.—The enolate solution, prepared from 6.6 mmol of MeLi and 387 mg (1.9 mmol) of the enol acetate **9** in 4.0 ml of 1,2-dimethoxyethane, was stirred at 25° and aliquots were removed periodically and quenched in Me_3SiCl. The mixtures were subject to the previously described isolation and analytical procedures to give the results indicated in eq K.

Copper-Catalyzed Decomposition of Diazo Ketones. A. Materials.—Reaction of benzoyl chloride with excess ethereal CH_2N_2 in the presence of Et_3N[29] afforded α-diazoacetophenone (**17**) as yellow needles from hexane: mp 47.4–48.6° (lit.[29] mp 47.8–48.4°); ir (CCl_4) 2110 and 1635 cm^{-1} (α-diazo ketone); uv (95% EtOH) 252 mμ (ϵ 11,500) and 297 (12,000); nmr (CCl_4) δ 7.2–8.0 (5 H, m, aryl CH) and 6.15 (1 H, s, $COCHN_2$). A similar reaction of 8.704 g (59.3 mmol) of cyclohexanecarboxylic acid chloride with excess ethereal CH_2N_2 yielded 6.59 g (73%) of the diazo ketone **21** as yellow needles from pentane (at −20°): mp 14.5–16° (lit.[30] 11–13°); ir (CCl_4) 2130 and 1655 cm^{-1} (α-diazo ketone); nmr ($CDCl_3$) δ 5.31 (1 H, s, $COCHN_2$) and 0.8–2.5 (11 H, m, aliphatic CH).

Commercial samples of CuI and CuO were employed. The bis(di-*n*-butyl sulfide) complex of CuI was described previously,[31] pentafluorophenylcopper was obtained from Dr. W. A. Shepard,[32] and the triphenyl phosphite complex of CuI was obtained from Dr. J. San Filippo.[33] A mixture of 1.24 g (10 mmol) of $(MeO)_3P$, 1.90 g (10 mmol) of CuI, and 20 ml of benzene was refluxed for 8 hr and then filtered while hot and concentrated. The residual solid (2.63 g, mp 175–185°) was recrystallized from an Et_2O–$CHCl_3$ mixture to separate the trimethyl phosphite complex of CuI as white needles, mp 192–193° (lit.[34] 175–177°).

Anal. Calcd for $C_3H_9CuIO_3P$: C, 11.46; H, 2.88; Cu, 20.20; I, 40.35. Found: C, 11.54; H, 2.82; Cu, 20.12; I, 40.05.

A solution of the lithium enolate of acetophenone, prepared in the usual way from 37.2 mmol of MeLi, 7.15 g (37.2 mmol) of α-trimethylsiloxystyrene, and 38 ml of 1,2-dimethoxyethane, was treated with 6.62 g (37.2 mmol) of 3-bromocyclohexene. After the mixture had been stirred at 25° for 5 hr, it was partitioned between pentane and aqueous NH_4Cl. The organic layer was washed with H_2O, dried, concentrated, and distilled to separate 2.02 g (27%) of the **ketone 19** as a colorless liquid: bp 95–95.6° (0.1 mm); $n^{23}D$ 1.5508; ir (CCl_4) 1690 cm^{-1} (conjugated C=O); uv max (95% EtOH) 243 mμ (ϵ 11,300) and 280 (994); nmr (CCl_4) δ 7.2–8.2 (5 H, m, aryl CH), 5.74 (2 H, broad, vinyl CH), 2.6–3.1 (3 H, m, CH_2CO and allylic CH), and 1.1–2.3 (6 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 200 (14, M^+), 105 (100), 77 (40), and 43 (34).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.19; H, 8.20.

The cis isomer of 1,2-dibenzoylethylene (**20**), obtained by photoisomerization[35] of the commercially available trans isomer, crystallized as white needles: mp 132–133° (lit.[35] mp 134°); ir ($CHCl_3$) 1670 (conjugated C=O) and 1610 cm^{-1} (conjugated C=C); uv max (95% EtOH), 262 mμ (ϵ 17,100); nmr ($CDCl_3$) δ 7.3–8.2 (10 H, m, aryl CH) and 7.21 (2 H, s, vinyl CH); mass spectrum *m/e* (rel intensity), 236 (5, M^+), 105 (29), 78 (100), 77 (31), 52 (20), 51 (22), and 50 (16).

B. Reaction of the Diazo Ketone with Cyclohexene.—A mixture of 6.5 g (45 mmol) of the diazo ketone **17**, 1.00 g (5.3 mmol) of CuI, and 250 ml of cyclohexene was heated under reflux. After 40 min a vigorous exothermic reaction occurred which consumed all the diazo ketone within 10 min. During this time, the color of the reaction mixture became very dark. The reaction mixture was filtered and the filtrate was concentrated and distilled to separate 2.46 g (28%) of the crude cyclopropyl ketone **18** as a pale yellow liquid, bp 96.5–99° (0.1 mm), $n^{25}D$ 1.5602 [lit.[36] bp 145° (1 mm)], which contained (glpc, Versamid 900 on Chromosorb P) *ca.* 10% of lower boiling impurities. A pure sample of the ketone **18** was collected (glpc) as a colorless liquid: $n^{25}D$ 1.5629; ir (CCl_4) 1670 cm^{-1} (conjugated C=O); uv max (95% EtOH) 245 mμ (ϵ 17,100); nmr (CCl_4) δ 7.2–8.2 (5 H, m, aryl CH), 2.2–2.5 (1 H, m, COCH), and 1.1–2.2 (10 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 200 (53, M^+), 157 (81), 105 (100), 77 (82), 51 (29), 44 (75), 43 (84), and 39 (27).

The stereochemistry assigned to the cyclopropyl ketone **18** was based upon its preparation[37] from derivatives of the known

(28) In an experiment where a solution of the enolate **8** was added slowly to excess Ac_2O, none of the C-acylated product **10** was detected. This suggests that diketone **10** is formed by reaction of the enolate **8** with the initially formed enol acetate **9**.

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acid 24a. To verify this assignment, the ketone 18 (704 mg or 3.5 mmol) was oxidized with peroxytrifluoroacetic acid [from 12 mmol of $(CF_3CO)_2O$ and 10 mmol of H_2O_2] in 7.5 ml of CH_2Cl_2 containing 3.55 g (25 mmol) of suspended Na_2HPO_4. After the mixture had been refluxed for 12 hr, it was filtered and the filtrate was washed with aqueous Na_2CO_3 and then concentrated. The residual pale yellow liquid (501 mg) contained (glpc, Versamide 900 on Chromosorb P) a component believed to be the ester 25 [*ca.* 50%, retention time 14.6 min, ir (CCl_4) 1730 cm^{-1} (conjugated ester)], the ester 24b [*ca.* 25%, 17.6 min, ir (CCl_4) 1750 cm^{-1} (ester C=O)], and the starting ketone 18 (*ca.* 25%, 20.2 min, identified by ir and glpc retention time). The phenyl ester 24b was selectively saponified by stirring a solution containing the crude esters 24b and 25 and 2.0 ml of aqueous 0.5 *M* KOH in 10 ml of EtOH at 25° for 2 hr. The crude acidic product was separated by appropriate extractions and recrystallized from hexane to separate 25 mg (5.1% based on the starting ketone 18) of the acid 24a as white needles, mp 94.8–96° (lit.[38] 96.5°), identified with an authentic sample by a mixture melting point and comparison of ir spectra. To obtain an authentic sample of this acid 24a for comparison, ethyl diazoacetate was decomposed in boiling cyclohexene in the presence of suspended copper powder. The crude ethyl ester 24c [bp 111–115° (18 mm), $n^{25}D$ 1.4631–1.4642] was saponified (KOH in EtOH–H_2O) and the acid was recrystallized from hexane: mp 95–96.2°; ir (CCl_4) 1695 cm^{-1} (carboxyl C=O); nmr (CCl_4) δ 1.0–2.2 (multiplet, aliphatic CH); mass spectrum *m/e* (rel intensity) 140 (43, M^+), 105 (31), 97 (49), 95 (42), 86 (49), 81 (37), 80 (100), 79 (31), 68 (33), 67 (45), 55 (46), 41 (51), and 39 (46).

The quantitative experiments summarized in eq L were performed by adding 0.034 mmol of the indicated catalyst to solutions of 100 mg (0.69 mmol) of the diazo ketone 17 in 5.0 ml of cyclohexene. The progress of the reactions was monitored by use of the ir absorption at 2110 cm^{-1} characteristic of the starting diazo ketone. When the diazo ketone was consumed, the mixtures were partitioned between PhH and aqueous NH_4Cl containing NH_3. The organic extracts were mixed with known amounts of an internal standard (2-phenylnaphthalene) and analyzed (glpc, silicone gum, SE-52, on Chromosorb P). The retention times were: ketone 19, 10.2 min; ketone 18, 12.7 min; 2-phenylnaphthalene, 17.1 min; and the *cis*- and *trans*-1,2-dibenzoylethylenes 20 (not resolved), 27.0 min. Collected samples of each component were identified with authentic samples by comparison of glpc retention times and ir spectra.

C. Reaction of the Diazo Ketone 21 with Cyclohexene.—A solution of 2.73 g (17.9 mmol) of the diazo ketone 21 in 30 ml of cyclohexene at 23° was treated with 87 mg (0.18 mmol) of $(n\text{-}Bu_2S)_2CuI$. An immediate exothermic reaction occurred and the color of the solution changed from pale yellow to dark brown. After 10 min the reaction had subsided and all the diazo ketone 21 had been consumed (ir analysis). The reaction solution was concentrated and a solution of the residue (2.88 g) in petroleum ether (bp 30–60°) was cooled to separate 272 mg (6%) of the enedione 23, mp 87–88.5°. After this material had been washed with aqueous NH_4Cl and NH_3, recrystallization afforded the pure enedione 23 as pale yellow needles: mp 88–89.5°; ir (CCl_4) 1685 (conjugated C=O) and 990 cm^{-1} (trans CH=CH); uv max (95% EtOH) 234 mμ (ϵ 12,500) and 349 (96); nmr ($CDCl_3$) δ 7.03 (2 H, s, vinyl CH), 2.3–3.0 (2 H, m, CHCO), and 0.9–2.3 (20 H, m, aliphatic CH_2); mass spectrum *m/e* (rel intensity), 248 (1, M^+), 137 (20), 83 (54), 55 (99), 43 (26), 41 (100), and 39 (30).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.10; H, 9.82.

The mother liquors remaining after crystallization of the enedione 23 contained (glpc analysis, silicone fluid, no. 710, on Chromosorb P) the norcarane 22 (retention time, 10.4 min), the enedione 23 (retention time, 42.4 min), and two minor unidentified components (retention times, 9.2 min and 21.5 min). A sample of the norcarane 22 was collected (glpc) as a colorless liquid, which crystallized on cooling. Recrystallization from pentane gave the pure norcarane 22 as colorless needles: mp 36–37.5°; ir (CCl_4) 3030 (cyclopropyl CH) and 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.9–2.6 (multiplet); mass spectrum *m/e* (rel intensity), 206 (22, M^+), 123 (100), 95 (39), 83 (23), 81 (23), 67 (22), 55 (63), and 41 (43).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.23; H, 10.68.

(38) H. Musso and U. Biethan, *Chem. Ber.*, **97**, 2282 (1964).

A portion of material from the mother liquors was also subjected to a short-path distillation to separate the bulk of the norcarane 22. The residue (1.64 g) from the distillation was chromatographed on 100 g of alumina (activity grade III) with mixtures of hexane and Et_2O as the eluent. From ir and nmr analysis of the various fractions we conclude that the major component in the mixture is the enedione 23. The latter fractions from the chromatograph contained small amounts of material with ir and nmr spectra corresponding to the triketone 27 and the subsequently described tetramer.

In comparable decompositions of the diazo ketone 21 in cyclohexene, catalyzed by the heterogeneous catalysts CuO or CuI, the major volatile product (glpc) was the norcarane 22. To obtain the products from reaction of the diazo ketone 21 with $(n\text{-}Bu_2S)CuI$ a cold (5°) solution of 2.158 g (14.2 mmol) of the diazo ketone 21 in 60 ml of cyclohexane was treated with 7.021 g (14.5 mmol) of $(n\text{-}Bu_2S)_2CuI$ and the resulting solution was allowed to warm slowly. Evolution of N_2 began at about 7° and continued for 10 min, during which time the color of the solution changed from pale yellow to brown; ir analysis indicated that the reaction was complete after 30 min. The reaction solution was diluted with pentane, washed with aqueous NH_4Cl and NH_3, dried, and concentrated. The residual liquid (5.87 g) contained (glpc and tlc) n-Bu_2S, the keto thioether 26, and the cyclopropane 27 as well as a number of minor unidentified components. Chromatography on 102 g of alumina (activity grade III) separated 0.26 g of the crude sulfide 26 and 0.36 g of the crude cyclopropane 27, mp 80–110°. A collected (glpc, silicone gum, SE-52, on Chromosorb P) sample of the keto sulfide 26 was obtained as a colorless liquid: $n^{25}D$ 1.4915; ir (CCl_4) 1705 cm^{-1} (C=O); uv max (95% EtOH) 214 mμ (ϵ 720), 245.5 (449), and 305 (285); nmr (CCl_4) δ 3.16 (2 H, s, $COCH_2S$) and 0.8–3.0 (20 H, m, aliphatic CH); nmr [CCl_4 + Eu(DPM)$_3$] δ 8.02 (2 H, s, $COCH_2S$), 6.77 (1 H, m, CHCO), 5.16 (2 H, t, J = 7.0 Hz, CH_2S), 4.6–5.0 (4 H, m, CH_2), 2.1–2.9 (6 H, m, CH_2), 1.1–1.8 (2 H, m, CH_2), and 0.83 (3 H, t, J = 6.5 Hz, CH_3); mass spectrum *m/e* (rel intensity) 214 (2, M^+), 83 (100), 61 (24), 55 (69), 41 (66), and 39 (21).

Anal. Calcd for $C_{12}H_{22}OS$: C, 67.23; H, 10.34. Found: C, 67.50; H, 10.42.

Crystallization of the crude cyclopropane from hexane afforded the pure triketone 27 as white needles: mp 111–112°; ir (CCl_4) 1715 (shoulder) and 1695 cm^{-1} (C=O); uv max (95% EtOH) 289 mμ (ϵ 177); nmr ($CDCl_3$) δ 2.89 (1 H, t, J = 5.5 Hz, CHCO), 2.50 (2 H, d, J = 5.5 Hz, CHCO), and 0.9–2.6 (33 H, m, aliphatic CH); nmr [CCl_4 + Eu(DPM)$_3$] δ 3.88 (1 H, t, J = 5.5 Hz, trans COCH), 3.48 (2 H, d, J = 5.5 Hz, cis COCH), and 0.8–3.0 (33 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity), 372 (1, M^+), 289 (26), 95 (21), 83 (97), 55 (100), 41 (63), and 39 (19).

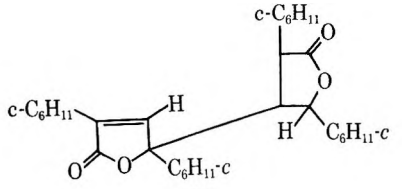
Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.10; H, 9.62.

The mother liquors remaining after crystallization of the triketone 27 were subjected to a series of fractional crystallizations from hexane to separate 33.4 mg of a tetramer as white needles: mp 159–160° (recrystallization raised the melting point to 161–162°); ir (CCl_4) 1762 (strong) and 1710 cm^{-1} (medium); uv max (95% EtOH) 214 mμ (ϵ 25,000) and 289 (110); nmr ($CDCl_3$) δ 7.06 (1 H, s), 4.08 (1 H, m), and 0.6–2.9 (*ca.* 46 H, m); mass spectrum *m/e* (rel intensity) 496 (6, M^+), 413 (10), 312 (15), 249 (12), 248 (10), 247 (30), 111 (23), 83 (100), 55 (66), and 41 (37).

Anal. Calcd for $C_{32}H_{48}O_4$: C, 77.37; H, 9.74. Found: C, 77.56; H, 9.90.

These data and earlier investigations of the products from the thermal or photolytic decomposition of α-diazo ketones[15d,39] suggest that our tetramer may have the structure 37. Our uv data are consistent with the value [λ_{max} 212 mμ (ϵ 11,300)] reported[39a] for conjugated lactone 38 and our nmr data indicate the presence of one vinyl CH and one >CHO function. Relatively abundant fragments in the mass spectrum at *m/e* 249 and 247 are compatible with the fragmentation of the molecular ion from 37 to form 39 and 40, and such a fragmentation process is supported by the presence of a metastable ion at *m/e* 125.0 (calcd $249^2/496$ = 125.0). The presence of strong ir absorption

(39) (a) K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, **76**, 5367 (1954); (b) P. Yates and T. J. Clark, *Tetrahedron Lett.*, 435 (1961); (c) R. Huisgen, H. König, G. Binsch, and H. J. Sturm, *Angew. Chem.*, **73**, 368 (1961).



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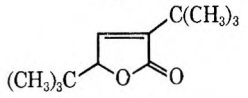

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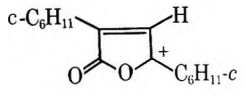
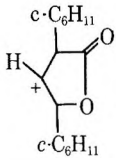


39 (*m/e* 247)



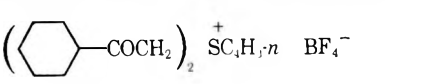
40 (*m/e* 249)

at 1762 cm^{-1} is also consistent with the presence of a γ-lactone and an α,β-unsaturated γ-lactone;[40] it is not clear whether or not the medium-intensity peak at 1710 cm^{-1} in the ir should be attributed to Fermi resonance.[41]

In a similar experiment, a cold (−15°) solution of 0.28 mmol of the diazo ketone **21** and 0.34 mmol of $(n\text{-}Bu_2S)_2CuI$ in a mixture of 0.50 ml of pentane and 0.15 ml of tetramethylsilane was placed in an nmr probe and the temperature of the solution was slowly raised to 0°. Comparable observations were made with separate solutions of the diazo ketone **21** and the $(n\text{-}Bu_2S)_2CuI$. The nmr singlet at δ 5.39 (at −15°) [δ 5.26 at 0°], attributable to the grouping $COCHN_2$, and the triplet (J = 7 Hz) at δ 2.53, attributable to the CH_2S grouping, were essentially the same in solutions of the separate components and the mixture. The diazo ketone signal at δ 5.26 was observed to diminish slowly and disappear as the solution was allowed to stand at 0°, but no new low-field nmr signal was observed during this period.

To obtain an authentic sample of the keto thioether **26**, a solution of 1.37 g (8.9 mmol) of the crude diazo ketone **21** in 10 ml of *n*-BuSH was treated dropwise with BF_3–OEt_2 until gas evolution was no longer observed. The resulting mixture was concentrated and then partitioned between pentane and H_2O. After separation of an insoluble product (143 mg, mp 113–118°), the pentane solution was dried, concentrated, and distilled (0.5 mm and 50–80° bath) to separate 703 mg of liquid which contained (glpc) the keto thioether **26** and a number of other unidentified components. A collected (glpc) sample of the keto sulfide **26** was identified with the previously described sample by comparison of glpc retention times and ir spectra.

The pentane-insoluble product from this reaction was recrystallized from an acetone–pentane mixture to separate a product, believed to be the sulfonium salt **41**, as colorless needles:



41

mp 123–124°; ir ($CHCl_3$) 1705 cm^{-1} (C=O); uv max (95% EtOH) 231 mμ (ϵ 349) and 275 (172); nmr ($CDCl_3$) δ 4.77 (4 H, s, $COCH_2S$), 3.37 (2 H, t, J = 7 Hz, CH_2S), and 0.8–3.1 (29 H, m, aliphatic CH).

Anal. Calcd for $C_{20}H_{35}BF_4O_2S$: C, 56.35; H, 8.27. Found: C, 56.07; H, 8.41.

The quantitative data summarized in eq M were obtained by dissolving the appropriate amounts of the diazo ketone **21**, the catalyst, $(n\text{-}Bu_2S)_2CuI$, and a weighed amount of *n*-hexadecane (an internal standard) in either 35.0 ml of cyclohexene or a mixture of 5.0 ml of cyclohexene and 0.50 ml of 1,2-dimethoxyethane. The resulting solutions were warmed until decomposition began (*ca.* 7°) and allowed to stand at this temperature until all the diazo ketone **21** was consumed (ir analysis). The resulting solutions were then diluted with pentane, washed with aqueous NH_4Cl and NH_3, dried, concentrated, and analyzed (glpc, silicone gum, SE-52, on Chromosorb P, programmed temperature rise 5 deg/min from 90 to 230°). On the glpc column employed the retention times were: $n\text{-}Bu_2S$, 7.2 min; *n*-hexadecane, 22.9 min; the keto sulfide **26**, 24.9 min; a minor component believed to be the epimer of ketone **22**, 25.8 min; the ketone **22**, 26.8 min; the enedione **23**, 35.7 min. With the glpc equipment used the triketone **27** was not eluted. Collected (glpc) samples of the products **22**, **23**, and **26** were identified with authentic samples by comparison of glpc retention times and ir spectra, and the glpc equipment was calibrated with known mixtures of authentic samples.

Treatment of the Lithium α-Chloroenolates with a Copper(I) Complex. A. The Chloroenolate 16.—A solution of the lithium enolate **16** was prepared by adding a solution of 4.7 mmol of MeLi in 3.0 ml of Et_2O to 1.06 g (4.7 mmol) of the silyl enol ether **14**. After the ethereal solution had been stirred at 25° for 1 hr, it exhibited nmr absorption at δ 7.0–8.0 (5 H, m, aryl CH) and 5.58 (1 H, s, vinyl CH). For comparison, a solution containing 20 mmol of the lithium enolate of acetophenone (from α-trimethylsiloxystyrene) in 22 ml of Et_2O exhibited nmr peaks at δ 7.0–8.0 (5 H, m, aryl CH), 4.42 (1 H, s, vinyl CH), and 4.16 (1 H, s, vinyl CH). In a similar experiment, a cold (−16°), ethereal solution containing 4.7 mmol of the lithium chloroenolate was treated with 2.24 g (4.7 mmol) of $(n\text{-}Bu_2S)_2CuI$ and then centrifuged to remove a small amount of yellow precipitate (presumably MeCu). The nmr spectrum of the supernatant liquid was essentially identical with the previously described lithium chloroenolate spectrum except for the presence of additional multiplets at δ 2.5–2.8 and 1.3–1.9 attributable to the protons of Bu_2S. A similar solution was refluxed for 6 hr, allowed to stand at 25° for 12 hr, and then partitioned between benzene and an aqueous solution of NH_4Cl and NH_3. Analysis (glpc, silicone gum, SE-52, on Chromosorb P) of the benzene solution indicated the presence of $n\text{-}Bu_2S$ (retention time 3.2 min), the chloro ketone **13** (7.2 min), and a small amount of the silyl enol ether **14** (10.4 min); no peak was observed corresponding to 1,2-dibenzoylethylene **20** (28.4 min). A collected sample of the chloro ketone **13** was identified with an authentic sample by comparison of ir spectra and glpc retention times.

B. The Chloroenolate 8.—A solution of the lithium enolate **8**, prepared from 2.0 mmol of MeLi and 451 mg (1.94 mmol) of the silyl enol ether **12** in 0.5 ml of 1,2-dimethoxyethane, was cooled to −55° and then treated successively with 5.0 ml (48 mmol) of cyclohexene, 196 mg of *n*-hexadecane (an internal standard), and 762 mg (1.58 mmol) of $(n\text{-}Bu_2S_2CuI$. The resulting solution was warmed to 22° and stirred for 20 min, during which time the reaction solution darkened and a black solid separated. The reaction mixture was partitioned between pentane and an aqueous solution of NH_4Cl and NH_3. After the pentane extract had been dried and concentrated, analysis (glpc, silicone gum, SE-52, on Chromosorb P) indicated the presence of $n\text{-}Bu_2S$ (retention time 7.2 min), the chloro ketone **7** (100% yield, 11.4 min), *n*-hexadecane (22.1 min), and a very small unidentified peak (16.2 min); no peaks were observed corresponding to the cyclopropyl ketone **22** (25.8 min) or the enedione **23** (37.1 min). A collected (glpc) sample of the chloro ketone product **7** was identified with an authentic sample by comparison of ir spectra and glpc retention times.

A comparable experiment was performed with the lithium enolate **8** [from 2.0 mmol of MeLi and 436 mg (1.88 mmol) of the silyl enol ether **12**], 0.5 ml of 1,2-dimethoxyethane, 5.0 ml (48 mmol) of cyclohexene, and 44 mg (0.09 mmol) of $(n\text{-}Bu_2S)CuI$. The resulting solution was warmed to 25° and stirred; aliquots were removed periodically and subjected to the previously described isolation and analysis procedures. After 20 min, the yield of chloro ketone **7** was quantitative; after 140 min the yield of chloro ketone **7** was 72% and a minor unidentified component was detected (retention time 18.8 min), but no peaks were present corresponding to the cyclopropyl ketone **22** or the enedione **23**. A number of similar experiments with various copper(I) salts and various reaction and isolation conditions give comparable results.

Preparation of the α-Chloro-α-mercuri Ketone 35.—A mixture of 2.7 g (12.5 mmol) of HgO, 0.1 g (0.3 mmol) of $Hg(OAc)_2$, 5.8 g (25 mmol) of the silyl enol ether **12**, 1 ml of H_2O, and 5 ml of EtOH was warmed on a steam bath with mixing for 30 min. After the resulting white solid had been dissolved in 700 ml of boiling tetrahydrofuran and filtered, the filtrate was allowed to

(40) R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959).

(41) C. L. Angell, P. J. Krueger, R. Lauzon, L. C. Leitch, K. Noack, R. J. D. Smith, and R. N. Jones, *Spectrochim. Acta*, **15**, 926 (1959).

stand in the cold. The bisketo mercurial **35** separated as 1.8 g (28%) of white solid, mp 230–232° dec, ir (Nujol) 1665 cm^{-1} (C=O). We were unsuccessful in obtaining other spectra for this substance because of its insolubility.

Anal. Calcd for $C_{16}H_{24}Cl_2HgO_2$: C, 36.96; H, 4.56; Cl, 13.64; Hg, 38.59. Found: C, 37.21; H, 4.67; Cl, 13.66; Hg, 38.85.

When a sample of the mercurial **35** was thermally decomposed in a sealed melting point tube, the volatile liquid which distilled from the decomposing sample was collected and identified with an authentic sample of the chloro ketone **7** by comparison of ir spectra. No evidence of decomposition was observed when a slurry of the mercurial **35** in cyclohexene was refluxed for 6 hr. After the reaction mixture had been partitioned between pentane and an aqueous solution of NH_4Cl, KI, and HCl, the calculated yield (glpc analysis) of the chloro ketone **7** was quantitative.

The reaction of this bisketo mercurial **35** with excess AcCl yielded a mixture of products containing (glpc, Apiezon L on Chromosorb P) primarily the enol acetate **9** accompanied by lesser amounts of the chloro ketone **7** and several unidentified components. A collected (glpc) sample of this product **9** was identified with an authentic sample by comparison of ir spectra and glpc retention times.

Registry No.—**4**, 31151-32-3; **7**, 1892-09-7; **9**, 311180-45-7; **10**, 31151-34-5; **11**, 31180-46-8; **12**, 31151-35-6; **14**, 31151-36-7; **15**, 31151-37-8; **17**, 3282-32-4; **18**, 31152-14-4; **19**, 31151-39-0; **20**, 959-27-3; **21**, 31151-40-3; **22**, 31152-16-6; **23**, 31152-17-7; **24c** acid, 21448-77-1; **26**, 31151-41-4; **27**, 31152-19-9; **35**, 31151-42-5; **37**, 31151-43-6; **41**, 31152-20-2.

Conformational Analysis. LXXVI. The Perhydrodurenes[1-3]

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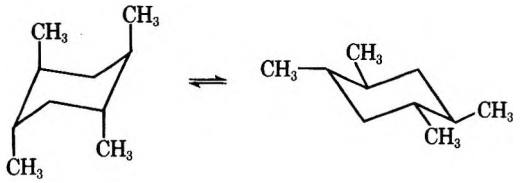
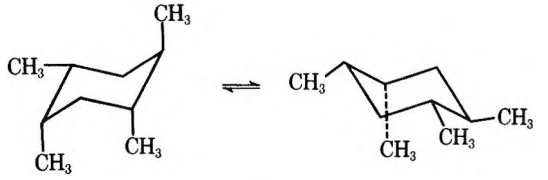
The five stereoisomeric perhydrodurenes (1,2,4,5-tetramethylcyclohexanes) have been prepared and equilibrated over palladium at elevated temperatures, and the thermodynamic quantities for the equilibria have been established. Nmr spectra of the compounds have been recorded, and structures have been assigned for each isomer.

While mono- and disubstituted cyclohexane rings have been extensively studied from the conformational point of view,[5] more highly substituted rings have been rarely examined.[6] It is known that with simple molecules conformational energies in general tend to be additive quantities; so with certain exceptions it is possible to determine *a priori* the relative energies of substituted cyclohexane systems. The present paper is concerned with extending this study experimentally to more complicated systems, specifically to the 1,2,4,5-tetramethylcyclohexane system. This particular ring system was chosen because it is reasonably typical of a polymethylated cyclohexane, there are five stereoisomers which can be individually examined, and each of them has a different energy. Thus it should be possible to assign unambiguously the structures of the isomers by studying the equilibrium between them. Finally, none of the energies is so high that it should not be possible to isolate all of the isomers from equilibrations at elevated temperatures.

The five isomers can be given the letters A–E for convenience of discussion. Each of these isomers is in principle an equilibrium mixture of two chair conformations, together with what is assumed to be a minor amount of boat forms. Thus, for isomer A, all of the methyl groups are equatorial, or they are all axial. For isomer B, one methyl is axial and the

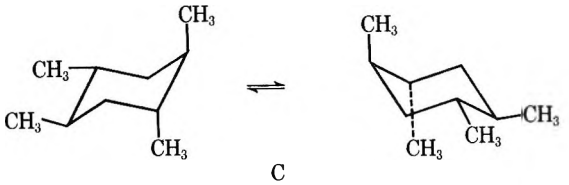


A

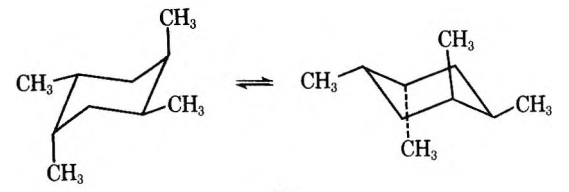


B

rest equatorial, or vice versa. Isomer C has two methyls equatorial and two axial, and the two conformations are superimposable mirror images. For isomer D, again two methyls are axial and two are equatorial in each conformation, and the conformations are in



C



D

fact superimposable. For isomer E, again there are two conformations which are superimposable, each contains two axial and two equatorial methyl groups.

(1) Paper LXXV: N. L. Allinger and J. C. Graham, *J. Org. Chem.*, **36**, 1688 (1971).

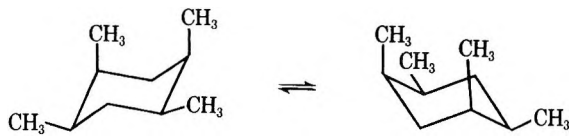
(2) Supported in part by Grant GP-15263 from the National Science Foundation.

(3) Abstracted from the Ph.D. dissertation of N.A.P., submitted to Wayne State University, May 1970.

(4) Correspondence concerning this paper should be addressed to this author at the University of Georgia, Athens, Ga. 30601.

(5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience–Wiley, New York, N. Y., 1965.

(6) C. J. Egan and W. C. Buss, *J. Phys. Chem.*, **63**, 1887 (1959).



E

With simple methylated cyclohexanes, it is well known that the energy of the system can be estimated (with some exceptions) by adding up the total number of gauche interactions in the system, multiplying by 0.9 kcal/mol, and thus obtaining a relative energy in the liquid phase. One exception which immediately comes to mind is the system which contains a 1,3-syn-diaxial dimethyl interaction. Such an interaction is known experimentally, again in the simple case, to total 5.5 kcal/mol (1.8 kcal/mol for two ordinary gauche interactions, and 3.7 kcal/mol for the methyl–methyl interaction).[7] In Table I, relative enthalpies of the conformations have been calculated in this way.

TABLE I
CONFORMATIONS AND ENTHALPIES OF 1,2,4,5-TETRAMETHYLCYCLOHEXANE[a]

Isomer	Conformation	No. of gauche[b] interactions (1,3-Me–H)	No. of syn-axial di-methyls[c]	Interaction, kcal/mol	ΔH, calcd kcal/mol
A	1a,2a,4a,5a	0	2	11.00	9.20
	1e,2e,4e,5e	2	0	1.80	0
B	1e,2e,4e,5a	4	0	3.60	1.80
	1a,2a,ea,5e	3	1	8.20	6.40
C	1a,2a,4e,5e	5	0	4.50	2.70
D	1a,2e,4a,5e	6	0	5.40	3.60
E	1a,2e,4e,5a	2	1	7.30	5.50

[a] Computed at 0.9 kcal/mol per gauche interaction. [b] Number of gauche butane interactions, excluding those associated with the 1,3-diaxial dimethyl interaction. [c] 5.5 kcal/mol per 1,3-diaxial methyl interaction, including two normal gauche interactions (1.8 kcal/mol) and one methyl–methyl interaction (3.7/kcal/mol).[7]

Since we wish to study equilibria, we must consider entropy differences as well as differences in enthalpy. With the usual assumption[8] that entropy differences between stereoisomers can be ascribed simply to differences in symmetry and mixing, we may calculate the relative entropies expected for isomers A–E. Isomers A and B are in principle mixtures of two conformations; however, the minor conformation has an enthalpy greater than the major one by 9.2 kcal in the first case and by 4.6 kcal in the second case. This means that the minor component will be present to a negligible extent and contribute nothing to the entropy of mixing. Isomers B and C, however, are *dl* mixtures, whereas the others are meso. Hence, there will be entropy due to the mixing of *dl* forms (R ln 2 favoring the *dl* isomer in each case). Finally, the symmetry numbers for isomers B, D, and E are each 1, while the symmetry numbers for isomers A and C are each 2. This means that isomers A and C will have $-R$ ln 2 entropy units contributed by symmetry. The calculated relative entropies thus obtained are given in Table II.

(7) N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, **83**, 2145 (1961).
(8) Reference 5.

TABLE II
ENTROPY DIFFERENCES IN 1,2,4,5-TETRAMETHYLCYCLOHEXANES[a]

Isomer	Meso or *dl*	Symmetry no., σ	Due to symmetry ($-R$ ln σ)	Due to mixing of *dl* forms (R ln 2)	Total calcd
A	Meso	2	−1.38	0	−1.38
B	dl	1	0	1.38	+1.38
C	dl	2	−1.38	1.38	0
D	Meso	1	0	0	0
E	Meso	1	0	0	0

[a] In eu.

Having now the enthalpies and entropies expected for the isomers A–E, we can calculate from the relationship $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$ for a given temperature what the free-energy differences will be, and from the relationship $\Delta G^\circ = -RT \ln K$, we can then calculate the equilibrium constants expected between each pair of isomers, and finally, from these equilibrium constants, we can calculate the percentage composition of an equilibrium mixture. The results are as shown in Table III for a temperature of 250°.

TABLE III
PER CENT ISOMERS AT EQUILIBRIUM (250°)
ESTIMATED LIQUID PHASE

A	51.76
B	36.75
C	7.72
D	3.25
E	0.52

Examination of these numbers shows that there are anticipated very large differences between each isomer, so that from the equilibrium data obtained experimentally, it should be possible to unambiguously assign the structures of these compounds.

Results and Discussion

Perhydrodurene was prepared by the hydrogenation of durene with platinum in acetic acid at room temperature. The equilibration was carried out in a manner similar to that used for other alkylcyclohexanes.[9] The equilibrations were conducted in sealed tubes with small amounts of palladium on carbon at temperatures ranging from 224 to 317°. The tubes were adequately filled (about 70–80% by volume) so that, when the equilibrium temperature was reached, the volume of material in the gas phase was nearly zero. This avoids the problem of the presence of a gas phase in which the equilibrium constant differs from that of the liquid.[9] The equilibrations were then quenched and the mixtures were analyzed by vapor phase chromatography several times. In each run five peaks were detected and labeled 1, 2, 3, 4, 5. These five peaks correspond to the isomers A, C, B, D, and E, respectively, and the data are summarized in Table IV.

The structures can be assigned unambiguously from the percentages present, as indicated in Table IV. The conformational rule suggests that the order of elution of the isomers on vpc should be the same as the order of isomer stability, and, with one exception, this was found to be the case. In addition, the hydrogenation

(9) N. L. Allinger, W. Szkrybalo, and F. A. Van-Catledge, *J. Org. Chem.*, **33**, 784 (1968); N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **81**, 4080 (1959).

TABLE IV
EXPERIMENTAL AMOUNTS OF ISOMERS A, B, C, D, AND E AT EQUILIBRIUM

Isomer	Fraction no.	% composition 224°	250°	274°	297°	317°
A	1	62.17	59.23	57.49	54.93	53.58
B	3	31.38	32.90	34.52	35.92	37.21
C	2	5.20	6.11	6.09	6.65	6.90
D	4	1.12	1.59	1.68	2.23	1.99
E	5		0.20	0.15	0.26	0.36

TABLE V
THERMODYNAMIC DATA FOR THE EQUILIBRIA
A ⇌ B, A ⇌ C, A ⇌ D, AND A ⇌ E[a]

Isomers at equilibrium	Calculated $\Delta H°$	Calculated $\Delta G_{298}°$	Calculated $\Delta S°$	Experimental $\Delta H°$	Experimental $\Delta G_{298}°$	Experimental $\Delta S°$
A ⇌ B	1.80	1.00	2.76	2.00 ± 0.04	1.20 ± 0.15	2.67 ± 0.08
A ⇌ C	2.70	2.30	1.38	2.58 ± 0.31	2.49 ± 0.40	0.32 ± 0.56
A ⇌ D	3.60	3.20	1.38	4.78 ± 0.92	4.25 ± 1.2	1.77 ± 1.69
A ⇌ E	5.50	5.10	1.38	6.77 ± 0.62	6.39 ± 1.2	1.26 ± 1.15

[a] Enthalpies and free energies in kcal/mol; entropies in eu.

of durene should yield a mixture of stereoisomers, in which the all-cis (E) product should predominate (von Auwers–Skita rule).[10] It was found that the hydrogenation product was a mixture of E (70.5%), B (24.4%), and D (5.1%).

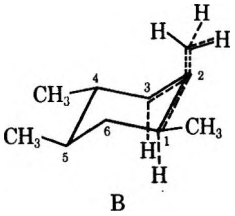
Having the equilibrium constants as a function of temperature, it is now easy to deduce the enthalpy and entropy changes which are experimentally found to relate the isomerizations. These data are summarized in Table V.

To confirm that all of the structures had been assigned correctly, small amounts of each isomer were isolated from the vapor phase chromatographic studies, and the nmr spectrum of each compound was determined. Since these molecules have various degrees of symmetry, considerable support for the structural assignments should be available from the nmr spectra. Some preliminary discussion of the nmr spectra of the 1,2-dimethylcyclohexanes at this point is appropriate. These compounds have been studied by several investigators.[11] Interestingly, the signal due to the methyl protons of *trans*-1,2-dimethylcyclohexane appears as an unresolved singlet. This fact has been explained in terms of identical chemical shifts for the axial methine proton and for the methyl group protons (the splitting of the methine proton by the adjacent methylene is swamped by the strong methyl singlet which is superimposed on it). This conclusion seems well established. On the other hand, the methyl protons of *cis*-1,2-dimethylcyclohexane are split into a doublet by their adjacent methine protons. In the cis isomer, because of the inversion of one chair form to the other, a given methyl spends half of its time in the axial and half in the equatorial position, and the two methyls become equivalent in the nmr. For comparison, *trans*-1,2-dimethylcyclohexane shows a broad absorption band at δ 1.20–1.80, integrating for 8 protons, and a sharp singlet at δ 0.92, integrating for 8 protons. The cis isomer shows a singlet at δ 1.42, integrating for 10 protons, and a sharp doublet at δ 0.835, integrating for 6 protons and showing a separation of 6.6 Hz.

The nmr spectrum of fraction 1 (assigned the structure of isomer A) consists of a large peak at δ 0.889 and two broad peaks at δ 1.516 and 1.616. The peak at δ 0.889 apparently stems from the methine protons plus the methyl protons and integrates for an area of 16 or 17 protons. The overall spectrum is quite strikingly like that of *trans*-1,2-dimethylcyclohexane, consistent with the assigned structure. Since the axial protons on a simple cyclohexane ring absorb at a higher field than do the equatorial,[12] the broad peak at δ 1.516 is probably due to the axial methylene protons, and the peak at δ 1.616 is due to the equatorial methylene protons.

The nmr spectrum of fraction 3 (Figure 1), assigned the structure of isomer B, consists of a broad region between δ 1.93–0.97, a large doublet (J = 1.5 Hz) at δ 0.853 which integrates for 12–13.5 protons, and a smaller, sharper doublet (J = 1.5 Hz) at δ 0.785 which integrates for 1.5–3 protons. The total integration for the two doublets is 14.5–15 protons.

Our interpretation of this spectrum is as follows. The signal at δ 0.785 represents one-half of the axial methyl doublet ($J \approx 6.8$ Hz); the other half is under the large peak at δ 0.853, together with the three equatorial methyls and three of the methine protons. From the chemical shifts of the peaks, compared with those of the dimethylcyclohexanes, the nmr is consistent with the structure B. Finally, the 1.5-Hz splittings observed at δ 0.785 and 0.853 can be interpreted by means of long-range coupling. Such coupling requires an "M" type of arrangement of the 4 σ bonds involved,[13] which are as shown by the dashed lines for isomer B. The axial protons at C-1 and at C-3 are



B

both oriented properly to couple with protons in the methyl group at C-2. The proton at C-1 probably has a chemical shift not too different from that of the axial methyl,[12] however, so that probably it is the axial proton at C-3 which is leading to the observed coupling.

(10) Summary and references: R. P. Linstead, W. v. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Amer. Chem. Soc.*, **64**, 1985 (1942).

(11) J. I. Musher, *Spectrochim. Acta*, **16**, 835 (1960); N. Muller and W. C. Tosch, *J. Chem. Phys.*, **37**, 1167 (1962); S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).

(12) H. Booth, *Tetrahedron*, **22**, 615 (1966).

(13) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

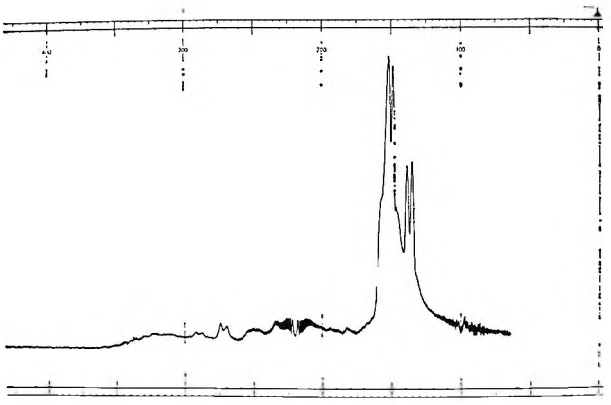


Figure 1.—100-MHz nmr spectrum of isomer B, 250-Hz sweep width.

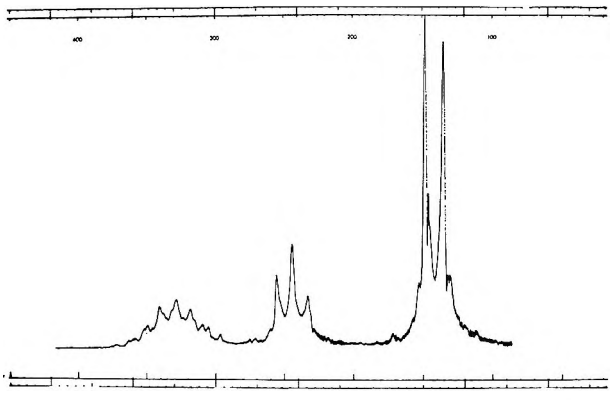


Figure 2.—100-MHz nmr spectrum of isomer D, 250-Hz sweep width.

Inspection of the structures of isomers C, D, and E shows that they have a good deal of similarity. Because of the high symmetry, each has many equivalent protons, and the differences between them are rather subtle. Therefore, all we are able to do here is show that the three spectra from fractions 2, 4, and 5 are consistent with the structures C, D, and E and thus consistent with the assignment of structure as determined from the energy relationships. The nmr spectra themselves are insufficient to prove which of these structures is which.

The nmr spectrum of fraction 4 (assigned structure D) consists of a doublet at δ 0.818 separated by 6.9 Hz, a triplet at δ 1.330 separated by 5.6 Hz, and a complex multiplet at δ 1.780 (Figure 2). These three absorptions integrate for 12, 4, and 4 protons, respectively. The first is clearly the methyl peak, which is split by coupling with the adjacent methine hydrogen. When D inverts, the axial and equatorial methyls are interchanged and so are the methine hydrogens. Hence the methyls are all equivalent. Similarly, the 4 methine protons are equivalent, and the 4 methylene protons are equivalent. There is more to the situation than that, however, because of the couplings between the protons.

The actual nmr spectrum at 100 MHz for isomer D is recorded in Figure 2. The detailed interpretation is as follows. The chemical shifts for the methyl, methylene, and methine protons are taken to be the values indicated respectively in the downfield direction.

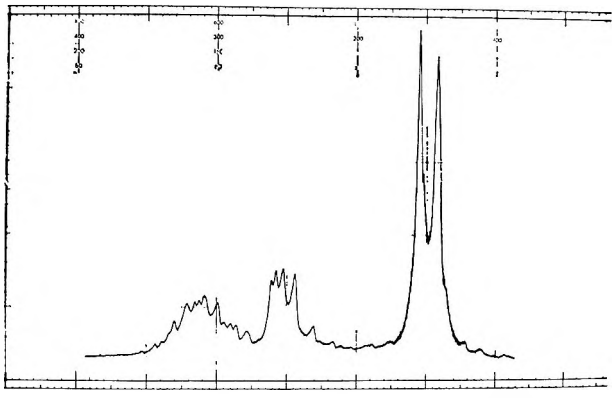


Figure 3.—100-MHz nmr spectrum of isomer E, 250-Hz sweep width.

Coupling constants (in hertz) are estimated by analogies, considering the dihedral angles from models, as follows.

$$J_{\text{methine-methine}} = 5.1$$

$$J_{\text{methylene-geminal}} = -12.0$$

$$J_{\text{methine-methylene-}trans} = 6.2$$

$$J_{\text{methylene-methine-}cis} = 5.0$$

These coupling constants and chemical shifts give a calculated spectrum for the methyl group which shows a large doublet, the downfield peak being slightly taller, separated by 6.9 Hz and each component of the doublet is split into a triplet, with about 80% of the intensity being in the center part. This is consistent with the rather broad base of the methylene doublet. Again, the calculations for the methylene part of the spectrum show a triplet with the center component being the largest, and the downfield component being larger than the upfield component, and then each of these components is further split, the center one into a triplet, and the other two into doublets. The overall separation between the components is 5.6 Hz, and the separation of the smaller peaks are of the order of 0.5 Hz. This is all quite consistent with the observed spectrum, where the resolution does not permit one to detect the fine structure.

The available program will not deal with a number of protons involved in calculation of the methine spectrum, but a first-order calculation, allowing for the coupling constants used predicts a quite complicated spectrum with 16 peaks, 8 of them being more intense than the other 8, and a detailed calculation would doubtlessly give an even more complex spectrum. Hence this calculation does not appear to be inconsistent with the observed spectrum, and the total spectrum is therefore taken to be consistent with the structure assigned.

For the spectrum which is assigned to compound E (Figure 3), the interpretation is rather similar to that given for the compound D. The methyl group appears as a doublet at δ 0.856, with a separation of 6.6 Hz. The methylene group appears as a multiplet, not very different from the triplet of isomer D. The geminal methylene protons are not necessarily identical in this case, but it looks as though they are nearly, but perhaps not quite, equivalent, which complicates the spectrum further.

Finally, the methine protons appear as a very com-

plex multiplet at δ 1.687. Again, this portion of the spectrum is beyond our ability to analyze. However, it is not inconsistent with what has been deduced up to this point. We may note that the methine protons are equivalent to one another, and there are only two kinds, of methylene protons: the pair which is cis to the adjacent methyls and the pair which is trans.

It is concluded that insofar as we can interpret the spectrum, it is consistent with the structure E. This spectrum should be similar to that of isomer D, but more complicated, due to the two sets of methylene protons instead of only one set.[14]

The spectrum assigned to isomer C (Figure 4) is quite different from the others. There is a doublet at δ 0.93 with a separation of 5.5 Hz, which integrates for 12 protons, and there is a poorly resolved doublet with peaks at δ 1.332 and 1.345 which integrates for 8 protons. The methyl groups are all equivalent in isomer C; so the chemical shift, splitting, and area of the peak at δ 0.923 is consistent with the methyl groups of this compound. The methylene and methine protons must by chance have almost identical chemical shifts. The methine protons are all equivalent to one another, and also the methylene protons are all equivalent to one another. This is conveniently seen using the postulate of Mislow and Raban and imagining deuterium substituted in turn for an axial and for an equatorial methylene proton at the same carbon. External rotations of the molecule together with ring inversion permit the two forms to be superimposed.[15]

If the chemical shifts of the methylene and methine protons in isomer C are accidentally equivalent (or almost so) in addition, then the very simple spectrum obtained is accounted for.

Experimental Section

1,2,4,5-Tetramethylcyclohexane (Mixture of Isomers).—To a 200-ml round-bottomed flask containing 13.4 g of durene dissolved in 75 ml of glacial acetic acid, 1.34 g of platinum oxide was added. The mixture was hydrogenated in an atmospheric hydrogenating apparatus. When the absorption of hydrogen became sluggish, the catalyst was removed and a fresh batch was added (1.34 g). This was repeated once or twice until the theoretical amount of hydrogen (7400 ml) was consumed, the sample was then diluted with 200 ml of water and extracted three times with three 50-ml portions of pentane. The pentane extracts were combined, washed with 10% sodium bicarbonate water, and dried over magnesium sulfate. The pentane was removed and the residue was distilled as a colorless liquid, bp 166–167.5°, wt 12.5 g (89.2%). Infrared analysis showed no C=C stretching but did show methyl bending at 1370 cm^{-1}. The tetranitromethane test for olefins was negative.

Anal. Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.50; H, 14.61.

Vpc Conditions for the Separation and Identification of Isomers. Procedure A.—(1) Varian Autoprep (Model 700); (2) a 20 ft × 3/8 in. aluminum column containing 30% SE-30 on Chromosorb W (45–60 mesh); (3) flow rate, 200 ml/min; (4) temperature, 120°; (5) relative areas of isomers were determined by the half-band width technique.

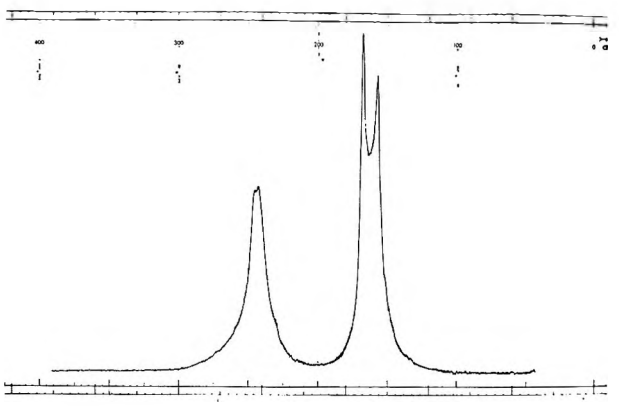


Figure 4.—100-MHz nmr spectrum of isomer C, 250-Hz sweep width.

Procedure B.—(1) F & M (Model 800); (2) a 39 ft × 0.25 in. aluminum column containing 30% SE-30 on Chromosorb W (60–80 mesh); (3) flow rate, 25 ml/min; (4) temperature, 175°; (5) relative areas of isomers were determined by the half-band-width technique.

Nmr Data Specifications.—The nmr spectra of the perhydrodurene isomers were taken with the Varian HA-100 (100 MHz) unless otherwise specified, although integrations were done on the A-60 (60 MHz) instrument. All perhydrodurene sample were diluted with carbon tetrachloride to make a 20% solution and were run at room temperature with TMS as the internal standard. The dimethylcyclohexane samples were diluted to 20% in chloroform with TMS as the internal standard.

Separation of a Hydrogenated Mixture of 1,2,4,5-Tetramethylcyclohexane Isomers.—The 1,2,4,5-tetramethylcyclohexane isomers obtained from the hydrogenation of durene were subjected to vpc analysis (procedure A). Three peaks were detected and isolated as fractions 1A, 2A, and 3A with retention times of 45.4 min (24.4% of the total), 54.0 min (5.1% of the total), and 57.0 min (70.5% of the total), respectively. These fractions were identified both by comparison of their retention times with those from the equilibrated samples and also by a comparison of the corresponding nmr spectra. The same perhydrodurenes were subjected to vpc analysis by procedure B. Three peaks were again detected with retention times of 140, 160, and 171 min.

Equilibration of 1,2,4,5-Tetramethylcyclohexane Isomers.—In a capillary tube, neat 1,2,4,5-tetramethylcyclohexane (mixture of isomers) was added along with 10% by weight of 10% palladium on carbon. The total amount of hydrocarbon was about 250 μl and occupied approximately 70–80% of the capillary's volume. The glass tube was sealed, immersed in a long stainless tube, and heated in an oven at the desired temperature for the desired length of time. Immediately upon removal from the oven, the stainless tube containing the sealed tube was quenched in ice water. The contents of the ampoule were analyzed by vpc (procedure B).

For each equilibration temperature, four sealed capillary tubes containing the hydrocarbon and catalyst were prepared and heated simultaneously. This was done so that the course of the equilibration could be followed by removal and vpc analysis of the contents of any of the four ampoules. Equilibrium was considered to have been reached when the amount of the main fraction detected by vpc did not change by more than 0.5% after 48 hr of heating.

In each run, five peaks were detected and labeled as fractions 1, 2, 3, 4, and 5, with retention times of 126, 136, 140, 160, and 171 min, respectively. Each sample was analyzed at least four times and the average value was taken, the average deviation being between 0.1–0.2% in each case. In Table IV, the relative amounts of all five fractions are tabulated for each equilibration temperature.

In order to illustrate reproducibility, a typical analysis of an equilibrated sample (12 days at 250°) monitored through the vpc several times is shown in Table VI. The thermocouple of the oven where the equilibrations were carried out was calibrated against three National Bureau of Standards thermometers.

(14) A referee has suggested that the energies of isomers D and E are sufficiently high that twist-boat forms may contribute significantly to the populations, since they would allow elimination of the severe 1,3-diaxial dimethyl interaction. This is correct. However, the entropies of the isomers are as calculated (to within the large experimental error, Table V), and other compounds that had to choose between the twist-boat or the 1,3-diaxial dimethyl interaction seem to have chosen the latter [ref 7, and B. L. Shapiro, *et al.*, *Tetrahedron Lett.*, 219 (1971)]. In any case, our arguments concerning the nmr spectra are unchanged. We assume rapid chair ⇌ chair interchange, and pseudorotation will lead to the same result as far as proton equivalencies are concerned.

(15) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

Calculated Spectra.—The calculated methyl and methylene nmr spectra of the perhydrodurene isomers were obtained through the use of a greatly modified version of the program by Stanley, Marquardt, and Ferguson, as modified by Scherr.[16]

TABLE VI

	% isomers				
Run no.	1	2	3	4	5[a]
1	59.13	6.12	32.97	1.78	
2	59.23	6.19	32.32	1.26	
3	59.52	6.06	32.62	1.80	
4	59.13	6.17	33.21	1.49	(0.20)
5	59.74	6.09	32.77	1.40	
6	59.25	6.10	32.84	1.81	
Av	59.33	6.12	32.96	1.59	

[a] The percentage of fraction 5 is an average value and is not totaled in with the percent of the other fractions.

Registry No.—A, 19899-39-9; B, 31328-42-4; C, 31328-43-5; D, 19899-42-4; E, 19903-06-1.

Acknowledgments.—The authors are greatly indebted to Dr. Paul Scherr, for the use of his program and for his advice and help in the calculation of nmr spectra to compare with the experimental spectra obtained in the present work; and to Dr. G. Karabatsos, for his kindness in helping us to obtain the 100-Hz nmr spectra.

(16) R. N. Stanley, O. W. Marquardt, and R. C. Ferguson, IBM Scherr Systems–SDA 3165 OPE NMR.

An Aminocyanoketenimine, Aminomalononitrile, and Aminocyanoimidazole from Diisobutene, Hydrogen Cyanide, and Hydrogen Fluoride. Preparation of Novel Diaminoethylenes and Diiminoethanes

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Reaction of 2,4,4-trimethylpentene-2 (TMP), with HCN and HF gave three novel products $(TMP)_n(HCN)_m$: (1) *tert*-octylaminocyanoketen-*N*-*tert*-octylimine (**1**) ($n = 2$, $m = 3$); (2) *tert*-octylaminomalononitrile (**12**) ($n = 1$, $m = 3$); and (3) 4-cyano-5-*tert*-octylaminoimidazole (**14**) ($n = 1$, $m = 4$). Reaction of **1** with $(CN)^-$ or HCN gave di-*tert*-octylaminomaleonitrile (**4**). Compound **4** was dehydrogenated by benzoyl peroxide to give di-*tert*-octyliminosuccinonitrile (**7**). With diethylamine **1** gave 2,3-di-*tert*-octylamino-3-diethylaminoacrylonitrile (**3**), which autoxidized to give 2,3-di-*tert*-octylimino-3-diethylaminopropionitrile (**6**). It is proposed that protonated **1**, **12**, and **14** are the end products of a thermodynamically controlled process in which *tert*-octylisonitrile is an intermediate. Biological and prebiological implications are discussed.

The following investigation is concerned with the mechanism and the novel products of the reaction of 2,4,4-trimethylpentene-2 (TMP), a diisobutene isomer, with hydrogen cyanide and hydrogen fluoride in the absence of additional nucleophiles.

These products are quite different from those obtained in the related Ritter reaction.[1] In that reaction, olefins are allowed to react with nitriles and nucleophiles, such as water in sulfuric acid medium.

A patent[2a] and two recent articles[2b] describe the use of HF in the Ritter reaction. In this modification HCN may be used as the nitrile. Depending on the nature of the olefin and the reaction conditions, formamides, imidoylfluorides, or trialkyl-substituted aminomalonamides were obtained.

Results and Discussion

The reaction consisted of an initial stage in which TMP was allowed to react with hydrogen cyanide and hydrogen fluoride. This stage was followed by a work-up stage in which unreacted hydrogen cyanide and hydrogen fluoride were removed, and the residue was added to a dipotassium hydrogen phosphate solution. The product was separated into three fractions: (1) the main fraction obtained from the pentane extracts of the crude reaction mixture; (2) a base-soluble by-product; (3) a crystalline high melting by-product.

The product composition was highly dependent upon reaction variables. No attempt was made to establish conditions for optimum yields of specific products.

Treatment of the main fraction with methanesulfonic acid resulted in the precipitation of a colorless salt. Treatment of this salt with concentrated aqueous KOH gave pure **1**. Elemental analysis and spectral data were consistent with *tert*-octylaminocyanoketen-*N*-*tert*-octylimine (Scheme I), $C_{19}H_{35}N_3$. The infrared spectrum showed a very strong band at 2025 cm^{-1} which is diagnostic of only the ketenimine group (>C=C=N–).[3]

The nitrile band is located at an anomalously low frequency (2180 cm^{-1}). A similarly displaced nitrile band is found in enaminonitriles[4] ($N{\equiv}CC{=}C\ddot{N}R_2$) and is ascribed to a considerable contribution of a charge-separated structure ($^-:\ddot{N}{=}C{=}CC{=}\overset{+}{N}R_2$) to the ground-state resonance hybrid. In the case of **1** the low frequency is probably due to analogous delocalization, involving a charge-separated structure $^-:\ddot{N}{=}C{=}CC{\equiv}\overset{+}{N}R$.

In the absence of protic reagents, **1** was stable at room temperature as judged by the constancy of the infrared spectrum.

Treatment of **1** with concentrated aqueous sodium cyanide gave a crystalline compound **4**.

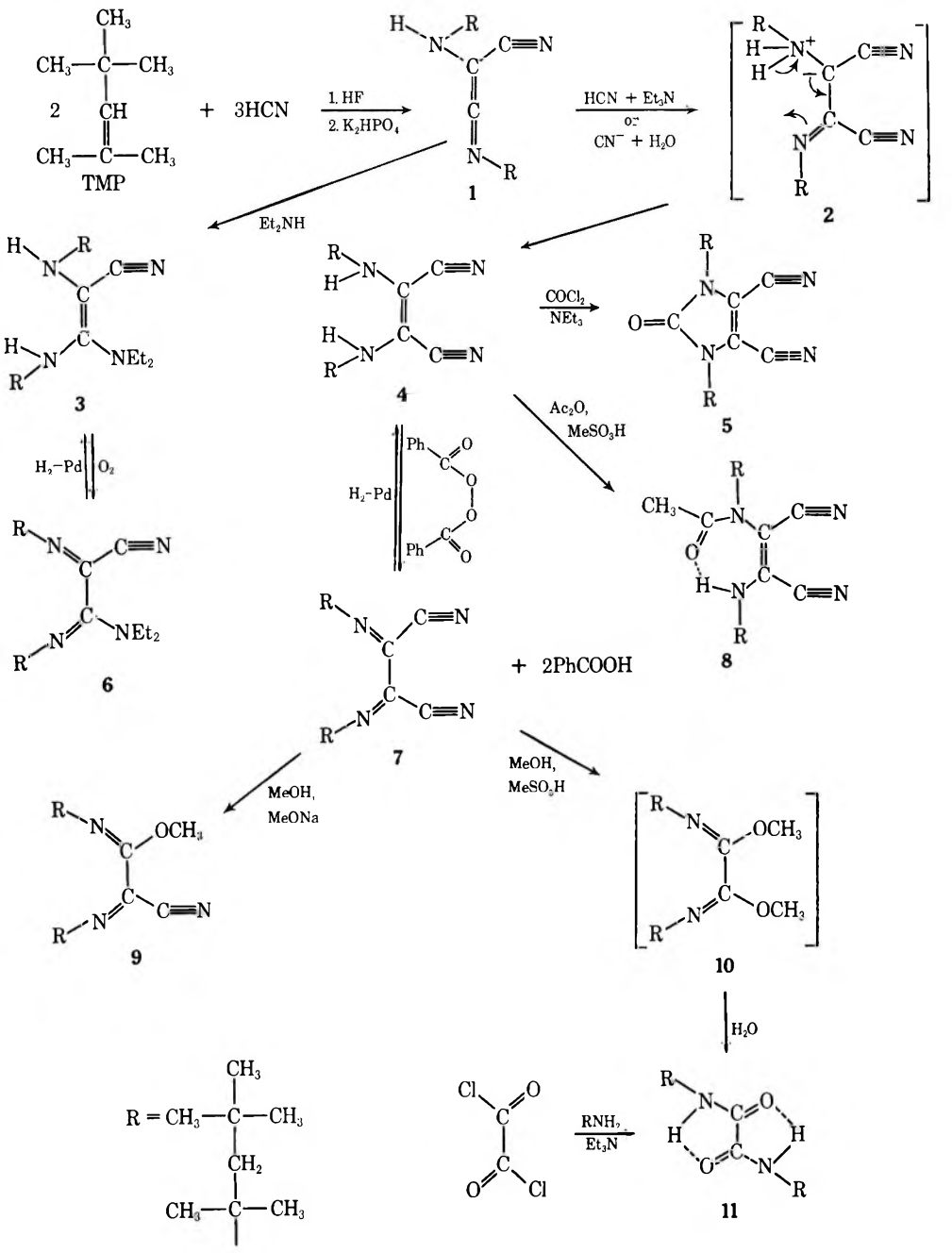
(1) L. J. Krimen and D. J. Cota, "The Ritter Reaction," Wiley, New York, N. Y., 1969, Chapter 3.

(2) (a) R. H. Potts, E. J. Miller, and A. Mais, British Patent 1,121,094 (1968); (b) J. R. Norell, *J. Org. Chem.*, **35**, 1611, 1619 (1970).

(3) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **77**, 3491 (1955).

(4) S. Baldwin, *J. Org. Chem.*, **26**, 3288 (1961).

SCHEME I



Elemental analysis and spectral data were consistent with di-*tert*-octylaminomaleonitrile, $C_{20}H_{36}N_4$ (Scheme I).

The frequencies of the C≡N (2190 cm^{-1}) and C=C (1575 cm^{-1}) bands are unusually low but are consistent with an enaminonitrile structure.[4]

When **1** was allowed to react with hydrogen cyanide in triethylamine at room temperature, **4** was also obtained.

Similarly, direct work-up of the reaction product of TMP with HCN and HF using triethylamine gave **4** in approximately 30% yield.

Upon exposure to atmospheric oxygen and light, **4** turned slowly orange. This orange material gave a strong epr signal whereas **4** did not. When **4** was treated in benzene solution with benzoyl peroxide, a bright orange color appeared, which faded after approximately 0.5 min. In a flow system in the epr spectrometer, an excellently defined, extremely strong epr spectrum was obtained (Figure 1), which persisted as long as the color remained. The spectrum is apparently due to a single radical species with a formation time and a decay time both of the order of several seconds.

When the reaction was run on a preparative scale, the color remained until 1 equiv of benzoyl peroxide had been added and then faded. From the resulting benzene solution, almost 2 equiv of benzoic acid and a colorless crystalline material **7** were obtained.

Elemental analysis and spectral data were consistent with di-*tert*-octyliminosuccinonitrile, $C_{20}H_{34}N_4$ (Scheme I).

The structure of **7** was proved by classical methods. Hydrolysis in methanol in the presence of methanesulfonic acid gave a compound **11** (Scheme I).

Mixture melting point determination, elemental analysis, and identity of infrared and nmr spectra proved **11** to be di-*tert*-octyloxamide.

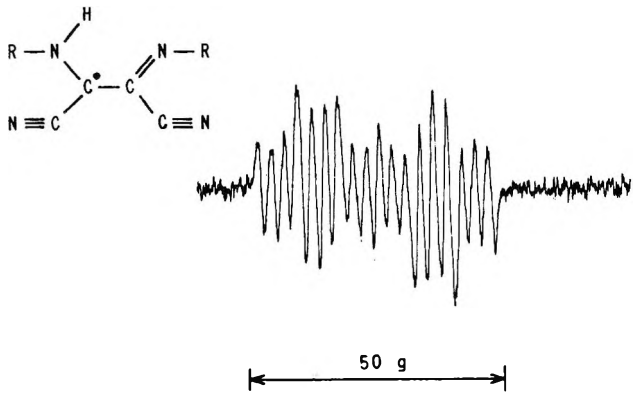
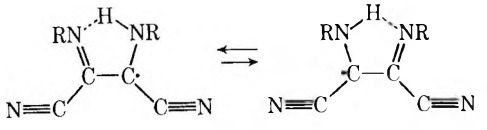


Figure 1.—Electron paramagnetic resonance spectrum of 4 + $(C_6H_5CO)_2O_2$.

The nitrile group in 7, which is a bisiminonitrile, should be displaceable by nucleophiles.[5] Under the reaction conditions, methanolysis probably first gives the bismethylimidate 10 (Scheme I) which then hydrolyzes to 11.

Catalytic hydrogenation of 7 gave a 90% yield of 4 so that the reaction by which 7 is made from 4 can be reversed in this manner (Scheme I).

The mechanism of the oxidation of 4 by benzoyl peroxide and the nature of the intermediate(s) has not been investigated.[6] In an apparently related reaction



of a tertiary enamine with benzoyl peroxide at room temperature a product containing a benzoyloxy group has been obtained.[7] In the oxidation of the flavins, which are structurally related to 4 (Scheme IV), two hydrogen atoms are similarly lost. The radical intermediates are the so-called flavin semiquinones.[3]

Further confirmation of the structure assigned to 4 comes from its ultraviolet spectrum. Compound 4 has uv max (isooctane) 308.0 mμ (log ε 4.23), in good agreement with the values observed for diaminomaleonitrile [uv max (EtOH) 300 mμ (log ε 4.15)],[9] the structure of which was unambiguously proven by X-ray analysis.[10]

Reaction of 4 with phosgene gave a crystalline product 5. Elemental analysis and spectral data were consistent with 1,3-di-*tert*-octyl-4,5-dicyano-2(3*H*)-imidazolone, $C_{21}H_{34}NO$ (Scheme I).

The formation of 5 suggests the cis configuration for 4 but does not prove it in view of the possibility of easy trans–cis isomerization. This possibility is inferred by the observed conversion of diaminofumaronitrile into diaminomaleonitrile.[11]

In CCl_4 solution 4 shows a strong C=C stretching band at 1675 cm^{-1}, which is also Raman active. This rules out C_{2h} symmetry and thus confirms the cis configuration.[12] The observed magnetic equivalence of the *tert*-octyl groups in 4 argues against an asymmetrical trans configuration with marked deviation from C_{2h} symmetry. Such a configuration was invoked to account for an anomalous C=C stretching band in the ir spectrum of diaminofumaronitrile taken in the crystalline state.[11] In solution such a rigid asymmetrical configuration could probably not exist due to removal of rotational restrictions.

It has not been established why the cis structure is so strongly preferred. Possibly the formation of 4 involves a cyclic rearrangement of an "ylide" intermediate 2 (Scheme I).

Alternatively, hydrogen bonding between the amino groups may be the reason. These amino groups are vinylogously related to the amino groups in cyanamide in which intermolecular hydrogen bonding is known to be strong.

The evidence presented thus far allows an unequivocal structure assignment to 1 as follows. (1) The structure of 7 has been proven by hydrolytic conversion to di-*tert*-octyl oxamide (11). (2) The structure of 4 is established because 4 is obtained by hydrogenation of 7. (3) The structure of 1 is established because addition of hydrogen cyanide to 1 gives 4. This structure assignment is furthermore supported convincingly by the spectral data.

Two further reactions of 7 and 4 deserve mention. When 7 was treated with sodium methoxide in methanol, a new compound 9 was obtained. Elemental analysis and spectral data were consistent with 2,3-di-*tert*-octylimino-3-methoxypropionitrile, $C_{20}H_{37}N_3O$.

Acetylation of 4 in acetic anhydride with methanesulfonic acid catalysis gave a crystalline monoacetylation product 8 according to elemental analysis and spectral data.[13]

All compounds discussed thus far have been derived from 4, which is the reaction product of 1 and HCN.

Compound 1 also reacts readily with diethylamine to give a crystalline compound 3. Elemental analysis and spectral data were consistent with 2,3-di-*tert*-octylamino-3-diethylaminoacrylonitrile, $C_{23}H_{46}N_4$ (Scheme I). Compound 3 was also obtained directly in 49% yield when diethylamine was used in the work-up of the reaction product of TMP with HCN and HF.

Compound 3 autoxidizes with remarkable facility. The product is a new compound 6. Elemental analysis and spectral data are consistent with 2,3-di-*tert*-octylimino-3-diethylaminopropionitrile, $C_{23}H_{44}N_4$. Compound 6 can be quantitatively reconverted to 3 by catalytic hydrogenation.

The ultraviolet spectra of 3 and 6 further support the assigned structures. In the spectrum of 3 a band at 275 mμ corresponds to an enaminonitrile chromophore (uv max 250–280 mμ)[4] and a band at 213 mμ to a conjugated enamine chromophore (uv max 220–240 mμ).[14]

(5) F. Kröhnke and H. M. Steuernagel, *Chem. Ber.*, **96**, 486 (1963).

(6) The cis configuration of 4 (*vide infra*) suggests the intriguing possibility that a pair of rapidly equilibrating hydrogen-bonded radical species is involved. This could account for the doublet nature of the epr spectrum.

(7) R. L. Augustine, *J. Org. Chem.*, **28**, 581 (1963).

(8) P. Hemmerich, C. Veeger, and H. C. S. Wood, *Angew. Chem.*, **77**, 699 (1965).

(9) R. L. Webb, S. Frank, and W. C. Schneider, *J. Amer. Chem. Soc.*, **77**, 3491 (1955).

(10) B. B. Penfold and W. N. Lipscomb, *Acta Crystallogr.*, **14**, 4589 (1961).

(11) Y. Yamada, N. Nagashima, Y. Iwashita, A. Nakamura, and I. Kumashiro, *Tetrahedron Lett.*, 4529 (1968).

(12) R. M. Bly, unpublished work.

(13) The unusual magnetic nonequivalences in the nmr spectrum of 8 are ascribed to asymmetry arising from slow rotation of the bulky *tert*-octyl groups which are attached to a seven-membered, hydrogen-bonded ring with high barriers to conformational interconversion. This aspect will be reported separately.

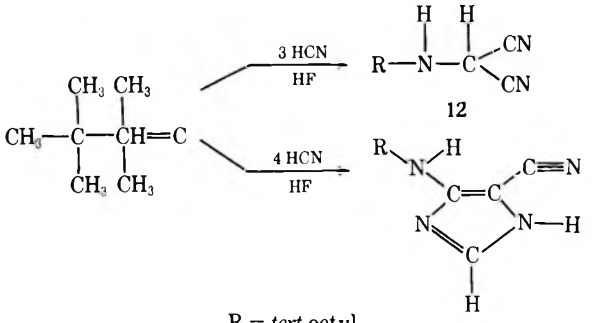
(14) G. Opitz, H. Hellmann, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 112 (1959).

The spectrum of **6** (uv max 237, 340 mμ) strikingly resembles that of the analogous **7** (uv max 234, 328 mμ).

The base-soluble by-product **12** from the reaction of TMP with HCN and HF was obtained as low-melting colorless crystals. It was purified through its methanesulfonic acid salt.

Elemental analysis and spectral data support the *N*-*tert*-octylaminomalononitrile structure, $C_{11}H_{19}N_3$ (Scheme II). In the mass spectrum the parent peak

SCHEME II



12 14

at mass 193 was absent; the first peak occurred at 178 (parent minus CH_3), and the dominant peak at mass 122 [parent minus $CH_2C(CH_3)_3$]. Amines often fail to show parent peaks,[15] and the above fragmentation pattern is in accordance with expectations. The ir spectrum showed a very weak nitrile band at 2200 cm^{-1}. The extreme weakness of this band agrees with Arnold's observation,[16] who could not discern the nitrile band in the ir spectrum of dimethylaminomalononitrile. The nmr spectrum showed two mutually coupled doublets assigned to NH and α CH. Both doublets disappeared upon exhaustive deuteration.[17]

Compound **12** is stable in the absence of oxygen. It is soluble in aqueous acid due to its alkylamino group and soluble in aqueous base due to the acidity of the hydrogen atom on the central carbon. Strong KOH causes precipitation of the crystalline salt, probably because of the common ion effect.

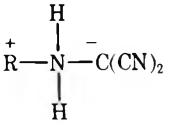
Work-up of the initial reaction product of TMP with hydrogen cyanide and hydrogen fluoride with a variety of reagents (KOH, $KHCO_3$, Et_3N, and Ph_3P[18]) yields, in all cases, a certain amount (yield ~4%) of a high-melting by-product **14**. According to elemental analysis, this product has the composition $C_{12}H_{21}N_4$ and, therefore, contains only a single TMP unit which has reacted with four molecules of hydrogen cyanide.

Spectral data, as well as the high melting point, suggest the 4-cyano-5-*tert*-octylaminoimidazole structure (Scheme II).

(15) F. W. McLafferty, *Anal. Chem.*, **34**, 26 (1962).

(16) Z. Arnold, *Collect. Czech. Chem. Commun.*, **26**, 1113 (1961).

(17) The exchange of CH as well as NH suggests a ylide intermediate **13**. This species is structurally analogous to trimethylammoniumdicyanomethylide, which was obtained as a stable compound by Arnold.[16]



13

R = *tert*-octyl

(18) The work-up with Ph_3P will be reported separately.

Compound **14** showed uv absorption at 248 mμ (log ε 4.03) in excellent agreement with the values reported by Ferris and Orgel[19] for unsubstituted 4-cyano-5-aminoimidazole [uv max (EtOH) 246 mμ (log ε 4.04)].

Mechanism.—The medium is highly acidic before the neutralization during the work-up. These conditions are singularly conducive to the accumulation of products of maximal thermodynamic stability (thermodynamic control).

It is postulated that the major product **1** is the result of a four-step process, each successive step resulting in the conversion of the intermediate or product formed in the preceding step into a new intermediate or product of increased thermodynamic stability. The steps involved in the ultimate formation of **1** are carbonium ion (step 1) → nitrilium ion (step 2)[20] → immonium ion (step 3) → ammonium ion (step 4). (See Scheme III.)

Ammonium ions are the most stable species obtainable under the reaction conditions. The principle of thermodynamic control also accounts for the apparent lack of products resulting from N-alkylation of a second molecule of HCN by the initial nitrilium ion, since this would give rise to another nitrilium ion which might not be more thermodynamically stable than the first one.

A molecule of TMP is first protonated to give a carbonium ion **15** (step 1) which adds a molecule of HCN to give the nitrilium ion or protonated isonitrile **16** (step 2).

HCN, which attacks through its nitrogen atom, is initially the only available nucleophile. However, once the nitrilium ion is formed, a protonation–deprotonation equilibrium with *tert*-octylisonitrile (**17**) can arise (step 2). The *tert*-octylisonitrile constitutes a second nucleophile which attacks protonated HCN **18** in the third step of the reaction to give, after an additional proton shift, the postulated intermediate **19**[21] (step 3) which is an immonium salt (protonated *tert*-octylformiminonitrile).

In the fourth step, **19** reacts with an additional molecule of *tert*-octyl isonitrile to give a new intermediate **20** which can stabilize itself to give an ammonium salt by three paths (a, b, and c), each of which leads to a protonated form of an isolated product. (a) Rearrangement of **20**, *via* path a, leads to the protonated aminocyanoketenimine **21**, which is the main product. (b) Loss of R^+ and subsequent protonation leads by path b to protonated *t*-octylaminomalononitrile **22** which is a by-product. (c) Reaction of **20** with an additional molecule of HCN leads to a cyclic intermediate **23** which is an ammonium salt that can be further stabilized by loss of R^+, rearrangement, and reprotonation (path c) to give protonated 4-cyano-5-*tert*-octylaminoimidazole (**24**), which is the second by-product.

The formation of **24** is assumed to take place before the addition of the work-up reagent because **24** is iso-

(19) J. P. Ferris and L. E. Orgel, *J. Amer. Chem. Soc.*, **88**, 3829 (1966).

(20) F. Johnson and R. Madroñero, *Advan. Heterocycl. Chem.*, **6**, 95 (1966).

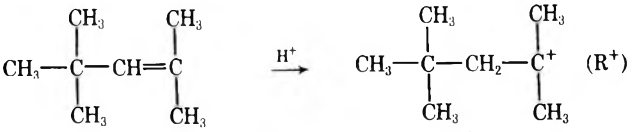
(21) It appears reasonable that in the strongly acidic solution HCN is also in equilibrium with "iso-HCN" through protonation–deprotonation (from carbon). "Iso-HCN" is expected to be far less stable than **17** because the hydride ion has a much greater migratory aptitude than the *tert*-octyl group. Therefore, the "iso-HCN" can easily revert to normal HCN by an intramolecular 1,2-hydride shift, thus keeping the concentration of "iso-HCN" quite low. Accordingly, unlike isonitriles, "iso-HCN" is not a stable compound and reactions involving it have not been reported thus far. The alternate possibility that **19** originates from the attack of "iso-HCN" on **16** appears therefore unlikely.

SCHEME III

REACTIONS BEFORE WORK-UP

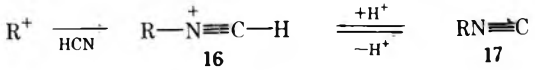
Steps 1–4 in Order of Increasing Thermodynamic Stability

Step 1: carbonium ion formation



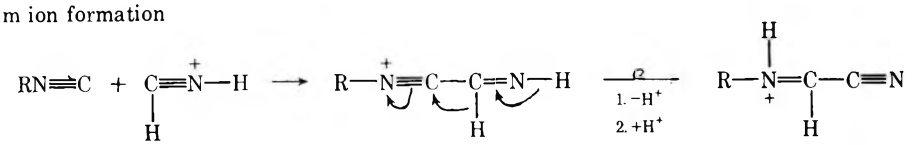
15

Step 2: nitrilium ion formation



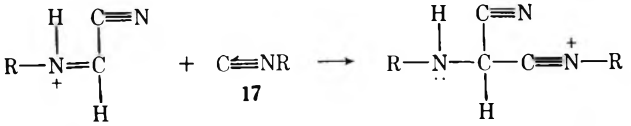
16 17

Step 3: immonium ion formation



18 19

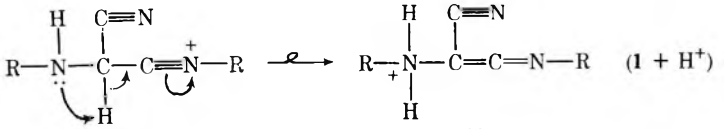
Step 4: ammonium ion formation



19 20

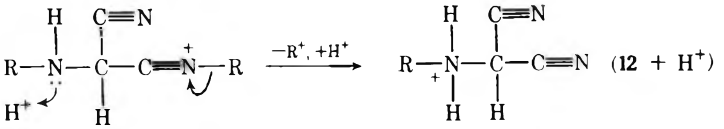
Paths a–c

Path a



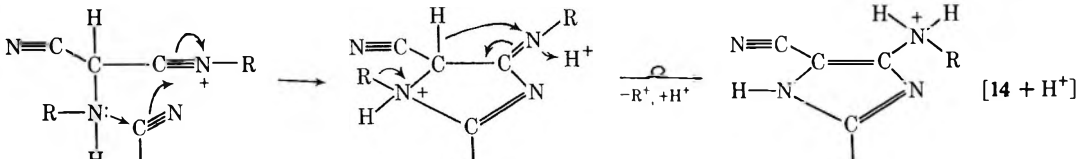
20 21

Path b



20 22

Path c



20 23 24

lated in approximately the same yield independent of the work-up reagent (KOH, Et_3N, Et_2NH). It is also obtained in the work-up with the highly nucleophilic but weakly basic reagent, triphenylphosphine.[18]

The first part of step 4, the reaction of an isonitrile **17** with an immonium salt **19**, is an example of a well-known reaction.[22]

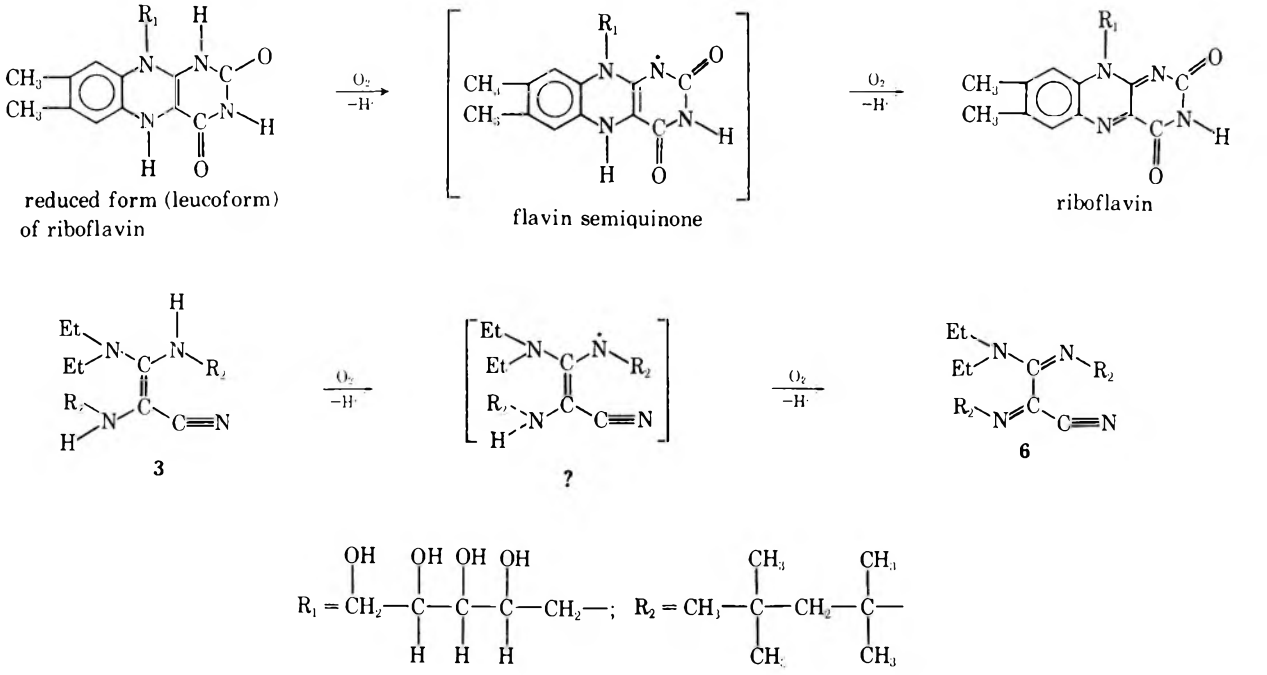
The second part of step 4, the rearrangement of intermediate **20** to give the protonated aminocyanoketenimine **21** (path a), is analogous to a standard method of synthesis for ketenimines which involves the elimination of HCl from imidoyl chlorides through the use of triethylamine.[23] In the present case, the reaction involves intramolecular proton abstraction by the *tert*-octylamino group.

Intermediate **19** in step 3 is obtained from the reac-

(22) I. Ugi, *Angew. Chem.*, **74**, 9 (1962).

(23) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **30**, 2564 (1965); P. Dimroth, German Patent 1,166,771 (1964); W. Ried and D. Junker, *Justus Liebigs Ann. Chem.*, **700**, 32 (1966); C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **76**, 4398 (1954).

SCHEME IV



tion of an isonitrile with a nitrilium ion (protonated HCN **18** in this case). This type of reaction, which is closely related to the preceding reaction of an isonitrile with an immonium ion, has also been described recently.[24]

Work-up with aqueous potassium hydroxide liberates **1** and **14** from their salts. Both compounds are evidently stable to hydrolysis under the strongly basic conditions. Compound **12** dissolved in the aqueous phase as its potassium salt and is freed by neutralization.

In the work-up with triethylamine **1** was a product when the excess of hydrogen cyanide was carefully removed *in vacuo* before the addition of the work-up reagent. This was apparent from the ir spectrum of the crude product, which prominently showed the characteristic ketenimine band at 2025 cm^{-1}.

When all unreacted hydrogen cyanide was not removed before addition of triethylamine, the ir spectrum of the product showed the absence of **1** (no absorption at 2025 cm^{-1}). Instead **4** was the main recovered product. These results indicate that initially produced **1** reacts with hydrogen cyanide to give **4**.

Implications in Biological and Prebiological Chemistry.—Most of the novel compounds are actually oligomers of HCN with one or two *tert*-octyl "handles." Therefore the reported work may provide a model for the otherwise intractable oligomerization of HCN itself.

Unsubstituted aminomalononitrile and aminocyanoimidazole, which are analogous to **12** and **14**, have been claimed as key intermediates in the prebiological oligomerization of HCN which presumably led to the purines.[14] These two compounds have not been obtained from synthetic oligomerization of HCN but have been prepared by alternate routes by Ferris and Orgel, who found aminomalononitrile too unstable for analysis.

By contrast **12** is stable in the absence of oxygen. In the presence of bases it decomposes rapidly with elimination of HCN. Evidence has been obtained that the other fragment is the novel intermediate *tert*-octylaminocyanocarbene.[25] Unsubstituted aminocyanocarbene has been proposed as an intermediate in prebiological peptide synthesis.[26] Its photochemical generation in a matrix at very low temperature has been claimed.[27]

The aminocyanoketenime **1** is remarkably stable at room temperature, but at high temperatures it undergoes a remarkable rearrangement to give *N*-*tert*-octyl-*tert*-octylmalononitrile as well as decomposition giving **12** as a primary product. Secondary thermolysis of **12** generates HCN which reacts with **1** to give **4**.[25]

Finally, I want to point out the striking relationship between **3** and vitamin B_2, riboflavin. The reduced form of riboflavin readily loses two hydrogen atoms upon exposure to atmospheric oxygen to give riboflavin in a process that closely resembles the autoxidation of **3** to give **6** (Scheme IV).

Experimental Section

Materials.—The 2,4,4-trimethylpentene-2 used was technical grade (95 mol % minimum) supplied by Phillips Petroleum Co. It was purified by treatment with $LiAlH_4$ in ether solution to reduce carbonyl-containing impurities, followed by distillation through a spinning-band column.

Hydrogen cyanide and hydrogen fluoride were obtained from Fumico, Inc., and The Matheson Co., respectively.

Reaction of 2,4,4-Trimethylpentene-2 (TMP) with HF and HCN.—A polyethylene reactor with a polyethylene condenser and magnetic stirrer was charged with 150 g (1.34 mol) of TMP (freshly distilled and dried over CaH_2) and 250 cc of dichloromethane (dried over CaH_2). The reactor was cooled to 0°, and the condenser was filled with ice. Then 155.3 cc (108.8 g, 4.02 mol) of HCN was distilled in, followed by 81.5 cc (80.7 g, 4.06 mol) of HF. The reaction mixture was stirred at room temperature for 2 hr. The solvent and unreacted HCN and HF were removed by sparging with nitrogen. The viscous yellow residue was transferred to a polyethylene addition funnel and

(24) T. Saegusa, N. Taka-Ishi, and Y. Ito, *J. Org. Chem.*, **34**, 4040 (1969).

(25) These reactions will be discussed in forthcoming publications.

(26) C. N. Matthews and R. E. Moser, *Nature*, **215**, 1230 (1967); *Proc. Nat. Acad. Sci.*, **56**, 1087 (1966).

(27) R. E. Moser, J. M. Fritsch, T. L. Westman, R. M. Kliss, and C. N. Matthews, *J. Amer. Chem. Soc.*, **89**, 5673 (1967).

was added during 25 min to a stirred mixture of 400 cc of pentane and a solution of 908 g of K_2HPO_4 in 1000 cc of water (external ice cooling).

The mixture was separated into three fractions: (1) an aqueous phase which was discarded; (2) a crystalline, high-melting precipitate, recovered by filtration; and (3) a pentane layer.

The pentane layer was extracted with two consecutive 200-cc portions of 20% aqueous KOH.

Methanesulfonic Acid Salt of *tert*-Octylaminocyanoketen-*N*-*tert*-octylimine (1 CH_3SO_3H).—After the KOH extraction the solvent was removed *in vacuo* from the above pentane solution, leaving 180.8 g of a light orange-colored oil. This residue was dissolved in 400 cc of anhydrous ether and cooled in an ice bath. Maintaining the cooling and under vigorous stirring, an ice cold solution of 55 g of anhydrous methanesulfonic acid in 150 cc of ether was slowly added. Immediately a precipitate started to form. After standing overnight in the refrigerator the supernatant was decanted. The remaining precipitate was washed by trituration with 300 cc of anhydrous ether followed by decantation, and this procedure was repeated four times. The washed, almost colorless precipitate was dried in a stream of dry nitrogen, yield ~166.8 g of essentially pure 1 CH_3SO_3H. For analysis a 10-g quantity of the salt was dissolved at room temperature in the minimum amount of anhydrous chloroform. A 100-cc quantity of anhydrous ether was added and crystallization started almost at once. After standing in the refrigerator overnight the colorless crystals were collected by filtration, washed with a small amount of anhydrous ether, and dried in a stream of dry nitrogen, yield ~8.04 g of the pure methanesulfonic acid salt of 1.

Anal. Calcd for $C_{20}H_{39}N_3SO_3$: C, 59.80; H, 9.81; N, 10.46; S, 7.98. Found: C, 59.65; H, 9.88; N, 10.36; S, 7.62.

The combined ether triturates were freed of solvent *in vacuo*, leaving 93 g of a residue which has not yet been investigated.

***tert*-Octylaminocyanoketen-*N*-*tert*-octylimine (1).**—A 25-g quantity of the methanesulfonic acid salt of 1 was dispersed in 150 cc of ether in a separatory funnel. Upon shaking with a cold concentrated KOH solution, the solid disappeared and the ether layer assumed a light yellow color. The aqueous layer was discarded, and the ether layer was dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo*. An 18.2-g quantity (96%) of 1 remained as a pale yellow oil, $n^{20}D$ 1.4851. This oil crystallized upon standing at −30° for 2 days: mp 14–16°; uv max (isooctane) 244, 315 mμ (log ε 4.13, 2.79); ir (neat) 3310 (m, NH), 2185 (m, C≡N), 2025 cm^{-1} (vs, C=C=N–); nmr (CCl_4) δ 1.00, 1.01 [18 H, 2 $C(CH_3)_3$], 1.18 [6 H, $C(CH_3)_2$], 1.43 [8 H, $C(CH_3)_2$ + CH_2], 1.61 (2 H, CH_2), 1.70 ppm (1 H, NH, disappears on deuteration); mass spectrum (70 eV) *m/e* parent 305; mol wt 307 (Thermonam).

Anal. Calcd for $C_{19}H_{35}N_3$: C, 74.68; H, 11.57; N, 13.75. Found: C, 74.21; H, 11.32; N, 13.73.

Reaction of 1 with $(C{\equiv}N)^-$. Di-*tert*-octylaminomaleonitrile (4). A. From Reaction of 1 with $(CN)^-$.—A 5.2-g quantity of crude 1 in ether solution was stirred for 2 hr with a concentrated aqueous solution of 5 g of sodium cyanide. The organic layer was then evaporated to dryness. The residue was crystallized from pentane at 0° and gave 3.85 g of crude 4, which was recrystallized once from hexane: mp 107.5–108°; uv max (isooctane) 308 mμ (log ε 4.23); ir (CCl_4) 3250 (m, NH), 2240 (m, C≡N), 2190 (s, C≡N), 1575 cm^{-1} (vs, C=N); nmr ($CDCl_3$) δ 1.02 [18 H, 2 $C(CH_3)_3$], 1.33 [12 H, 2 $C(CH_3)_2$], 1.60 (4 H, 2 CH_2), 3.54 ppm (2 H, 2 NH); mass spectrum (70 eV) *m/e* parent 332.

Anal. Calcd for $C_{20}H_{36}N_4$: C, 72.20; H, 10.92; N, 16.86; mol wt, 332.6. Found: C, 72.27; H, 11.00; N, 16.98 mol wt, 335 (Thermonam, acetone).

B. From Reaction of 1 and HCN in Triethylamine.–A 10-g quantity of crude 1 was dissolved in 20 cc of triethylamine, and 3 g of HCN was distilled in. After 2 hr, all volatiles were removed by sparging with nitrogen. The residue was recrystallized from methanol at −10° to give 4.6 g of a crystalline compound, which was identified as 4 by its ir spectrum and mixture melting point.

C. Directly from the Product of Reaction of TMP with HCN and HF.—Excess triethylamine was added to the cold reaction mixture obtained from 142 g (1.27 mol) of TMP, 51.0 g (1.89 mol) of HCN, and 38.0 g (1.92 mol) of HF. The volatiles were substantially removed by sparging with nitrogen and the residue was extracted with hot hexane, leaving the hydrogen fluoride salt of triethylamine undissolved. Cooling of the hexane extract to −10° gave a crystalline precipitate which was once recrystallized from hexane at −10° and once from methanol at −10°; 50 g (yield 31%, based on HCN) of 4 were obtained, mp 108°, ir spectrum identical with that of 4 obtained from 1. Also recovered were 5.3 g of a hexane-insoluble crystalline compound, which was identified as 14 (*vide infra*) by ir spectrum and mixture melting point determination.

Di-*tert*-octyliminosuccinonitrile (7).—A 9.45-g (0.039 mol) quantity of benzoyl peroxide dissolved in 50 cc of benzene was added dropwise with vigorous stirring to a solution of 13 g (0.039 mol) of 4 in 150 cc of benzene at room temperature. An orange color which developed upon the addition of the first drops of benzoyl peroxide solution remained until the addition was finished and then faded to light yellow within 1 min. The benzene solvent was removed *in vacuo*, and the residue was dissolved in hot hexane. Upon cooling 7.5 g (0.061 mol) of essentially pure benzoic acid (yield 78.4%) crystallized, identified by ir spectrum and mixture melting point with an authentic sample. The remaining benzoic acid was removed by washing with $NaHCO_3$ solution. Removal of the hexane *in vacuo* left a crystalline residue. Two recrystallizations from methanol (−10°) and one from hexane (−10°) gave 11.5 g (yield 88%) of 7: mp 65.5–67.0°; uv max (isooctane) 234.0, 328 mμ (log ε 4.15, 2.43); ir (CCl_4) 2220 (w, C≡N), 1625 cm^{-1} (s, C=N); nmr ($CDCl_3$) δ 0.97 [18 H, 2 $C(CH_3)_3$], 1.53 [12 H, 2 $C(CH_3)_2$], 1.85 ppm (4 H, 2 CH_2); mass spectrum (70 eV) *m/e* parent 330.

Anal. Calcd for $C_{20}H_{34}N_4$: C, 72.77; H, 10.38; N, 16.95; mol wt, 330.58. Found: C, 72.58; H, 10.15; N, 16.82; mol wt, 331 (Thermonam, acetone).

Hydrogenation of 7 to Give 4.—A 1-g quantity of 7 in ethyl acetate solution was hydrogenated using 75 mg of a 5% palladium-on-carbon catalyst. When 1 g-atom of hydrogen had been absorbed, the hydrogen uptake virtually stopped. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, 0.87 g of a crystalline residue remained which was identified as 4 by ir spectrum and mixture melting point determination.

Di-*tert*-octyl Oxamide (11) from 7.—A 2-g quantity of 7 was dissolved in 100 cc of methanol. To this solution was added 1 cc of water and 0.29 g of methanesulfonic acid, dissolved in 10 cc of methanol. The mixture was allowed to stand overnight at room temperature and was then poured into water. A crystalline precipitate formed which was recrystallized from a small amount of methanol at −30°. The product (1.58 g, yield 83.5%) was identified as di-*t*-octyl oxamide (11), mp 77–78.5°. The mixture melting point with an authentic sample of di-*tert*-octyl oxamide (prepared from oxalyl chloride and *tert*-octylamine) was undepressed and the ir and nmr spectra were identical with those of an authentic sample.

Anal. Calcd for $C_{18}H_{36}N_2O_2$: C, 69.16; H, 11.63; N, 8.96. Found: C, 69.48; H, 11.60; N, 8.97.

1,3-Di-*tert*-octyl-4,5-dicyano-2(3*H*)-imidazolone (5).—Into a Fisher–Porter bottle containing a magnetic stirring bar were introduced 5 g of 4, 20 cc of benzene, and 100 cc of triethylamine. The bottle was cooled to −30° and 5 cc of liquid phosgene was distilled into it. The bottle was then closed and the contents were stirred at room temperature for 72 hr. At that time the volatiles were removed by purging with nitrogen. The liquid residue was dissolved in pentane and chromatographed through a silica gel column. Unreacted 4 (2.1 g) was eluted with pentane–5% ether. From the 100% ether eluate 5 (1.8 g), mp 112.5–114°, was recovered: ir ($CHCl_3$) 2220 (m, C≡N), 1715 cm^{-1} (vs, C=O); nmr ($CDCl_3$) δ 0.90 [18 H, 2 $C(CH_3)_3$], 1.75 [12 H, 2 $C(CH_3)_2$], 2.05 ppm (4, H, $2CH_2$).

Anal. Calcd for $C_{21}H_{34}N_4O$: C, 70.33; H, 9.57; N, 15.62. Found: C, 69.97; H, 9.62; N, 15.45.

2,3-Di-*tert*-octylimino-3-methoxypropionitrile (9).—A 2-g quantity of 7 was dissolved in 100 cc of methanol. To this solution was added 20 cc of methanol containing 0.67 g of sodium methoxide. After 3 days at room temperature, the solvent was evaporated *in vacuo* and the residue was extracted with hot hexane.

Upon concentration and subsequent cooling (−50°) of this extract 0.8 g of crystalline 7 was obtained. A considerable amount of product remained dissolved in the hexane solution and did not crystallize even at −50°. This solution was chromatographed through a silica column. From the pentane eluate 0.67 g of 9 was recovered. It could be recrystallized from methanol at −50°, but the melting point was below room temperature: $n^{20}D$ 1.4686; ir (neat) 2210 (w, C≡N), 1690 and 1625 (m, two different C=N–), 1078 (s), and 985 cm^{-1} (s) ($COCH_3$); nmr (CCl_4) δ 0.94 and 0.96 [18 H, 2 $C(CH_3)_3$], 1.26 and 1.47 [each

6 H, 2 $C(CH_3)_2$], 1.57 and 1.77 (each 2 H, 2 CH_2), 3.63 ppm (3 H, OCH_3).

Anal. Calcd for $C_{20}H_{37}N_3O$: C, 71.57; H, 11.15; N, 12.52. Found: C, 71.71; H, 11.12; N, 12.33.

1-*tert*-Octylamino-2(*N*-*tert*-octyl)acetamidosuccinonitrile (8).—A 2-g quantity of **4** was dissolved in 40 cc of acetic anhydride containing 100 mg of methanesulfonic acid. The solution was allowed to stand at room temperature for 72 hr and was then added dropwise under stirring to 200 cc of concentrated potassium bicarbonate solution. This solution was extracted in a separatory funnel with three 30-cc quantities of benzene. Evaporation of the solvent *in vacuo* from the combined extracts left a crystalline residue.

After three recrystallizations from hot hexane, 0.93 g of **8**, mp 115.0–115.7° was obtained: ir (CCl_4) 3385 (m, NH), 2235 (m) 2195 (s) (C≡N), 1685 (vs, C=O), 1580 cm^{-1} (vs, C=C); nmr (100 MHz, $CHCl_3$) δ 0.98, 1.00 [18 H, 2 $C(CH_3)_3$], 1.42, 1.45, 1.49, 1.52 [12 H, four heterosteric CH_3, 2 $C(CH_3)_2$], 1.71, 1.72 [2 H, (heterosteric), CH_2], 1.68, 1.82, and 2.18, 2.32 [2 H (heterosteric), AB quartet, J = 14 Hz, CH_2], 4.80 ppm (1 H, NH, disappears upon deuteration).

Anal. Calcd for $C_{22}H_{38}N_4O$: C, 70.53; H, 10.24; N, 14.96. Found: C, 70.32; H, 9.98; N, 14.97.

The separations (in cycles) between the four heterosteric methyl resonances and the two heterosteric proton resonances (at 1.71 and 1.72 ppm) were dependent upon the applied field (100 MHz, 60 MHz), but the separations of the quartet resonances were unaffected.

2,3-Di-*tert*-octylamino-3-diethylaminoacrylonitrile (3). A. From Reaction of 1 with Diethylamine.—A 10-cc quantity of diethylamine was added to 10 g of crude **1** dissolved in 20 cc of triethylamine. There was an immediate exothermic reaction. After 1 hr at room temperature, all volatiles were removed *in vacuo*, and the residue was twice recrystallized from methanol at −30° to give 7.10 g of **3**: mp 51.0–52.5°; uv max (isooctane) 213, 275 mμ (log ε 3.91, 4.13); ir (CCl_4) 3310 (w, NH), 2170 (s, C≡N), 1580 (vs, C=C); nmr (CCl_4) δ 1.01, 1.03 [18 H, 2 $C(CH_3)_3$], 1.09 (t, J = 7 Hz, 6 H, 2 CH_2CH_3), 1.18, 1.26 [each 6 H, 2 $C(CH_3)_2$], 1.49, 1.52 (4 H, 2 CH_2), 1.89 (1 H, NH disappears upon deuteration), 3.22 (q, J = 7 Hz, 4 H, 2 CH_2CH_3), 4.95 ppm (1 H, NH, disappears upon deuteration); mass spectrum (70 eV) m/e parent 378.

Anal. Calcd. for $C_{23}H_{46}N_4$: C, 73.00; H, 12.27; N, 14.80. Found: C, 73.07; H, 11.87; N, 14.98.

B. From Product of Reaction of TMP with HCN and HF.—Excess diethylamine was added to the cold reaction mixture obtained from 71 g (0.635 mol) of TMP, 25 g (0.90 mol) of HCN, and 19 g (0.96 mol) of HF. All volatiles were removed by sparging with nitrogen, and the residue was extracted with hot hexane, leaving the hydrogen fluoride salt of triethylamine undissolved. Cooling of the hexane extract to −30° gave a crystalline precipitate which was recrystallized once from methanol (−30°) to give 57 g (yield 49% based on HCN) of **3**, melting point and ir identical with those of **3** prepared from **1**. Also recovered were 3.1 g of a crystalline, hexane-insoluble compound which was identified as **14** (*vide infra*) by ir spectrum and mixture melting point determination.

2,3-Di-*tert*-octylimino-3-diethylaminopropionitrile (6).—A 5-g quantity of **3** was allowed to stand for 48 hr at room temperature in contact with air. The originally colorless crystals deliquesced, and the product was a slightly yellow oil which was dissolved in pentane and chromatographed over an alumina column. Almost all of the product was eluted with pentane. After three recrystallizations from methanol (−30°), 3.55 g (yield 71%) of **6**, mp 28.0–29.5°, was obtained as light yellow crystals: uv max (isooctane) 237, 340 mμ (log ε 3.96, 2.92); ir (CCl_4) 2190 (w, C≡N), 1625 cm^{-1} (vs, C=N); nmr (CCl_4) δ 1.00, 1.02 [18 H, 2 $C(CH_3)_3$], 1.08 [t, 6 H, J = 7.4 Hz, $N(CH_2CH_3)_2$], 1.28 [6 H, $C(CH_3)_2$], 1.57 [8 H, CH_2 + $C(CH_3)_2$], 1.72 (2 H, CH_2), 3.24 ppm [q, 4 H, J = 7.4 Hz, $N(CH_2CH_3)_2$]; mass spectrum (70 eV) m/e parent 376.

Anal. Calcd for $C_{23}H_{44}N_4$: C, 73.32; H, 11.81; N, 14.87; mol wt, 376.71. Found: C, 73.71; H, 11.70; N, 14.43; mol wt, 375 (Thermonam, acetone).

Hydrogenation of 6 to Give 3.—A 1-g quantity of **6** in ethyl acetate solution was hydrogenated using 75 mg of a 5% palladium-on-carbon catalyst. When 1 equiv of hydrogen had been absorbed, the uptake virtually stopped. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, 0.93 g of a crystalline residue remained which was identified as **3** by ir spectrum and mixture melting point determination.

Methanesulfonic Acid Salt of N-*tert*-octylaminomalononitrile (12 CH_3SO_3H).—The two aqueous KOH extracts (I and II) obtained in the reaction of TMP with HF and HCN were separately neutralized by dropwise addition of concentrated (37%) hydrochloric acid (~50 cc) under stirring and external ice cooling. An orange-colored oil (crude *N*-*tert*-octylaminomalononitrile) separated, which was recovered from the aqueous layer by extraction with pentane followed by drying ($MgSO_4$) and removal of the solvent *in vacuo*, yield from extract I 4.54 g and from extract II 0.55 g. This residue (4.54 g) was dissolved in 30 cc of anhydrous ether and cooled in an ice bath. Maintaining the cooling and under vigorous stirring an ice-cold solution of 1.9 g of methane sulfonic acid in 30 cc of ether was slowly added. Immediately a precipitate formed. After standing in the refrigerator for 2 hr the supernatant was decanted. The precipitate was triturated with three 50-cc portions of anhydrous ether, collected by filtration, and dried in a stream of dry nitrogen, yield 5.38 g of essentially pure methanesulfonic acid salt of **12**. For analysis a small quantity of the salt was dissolved in an excess of cold acetonitrile; the solution was treated with charcoal, filtered, and concentrated *in vacuo* until crystallization started. After standing in the refrigerator for 2 hr the colorless salt was collected by filtration. It was stable at −10° but decomposed upon prolonged standing at room temperature.

Anal. Calcd for $C_{12}H_{23}N_3SO_3$: C, 49.79; H, 8.02; N, 14.52; S, 11.07. Found: C, 49.27; H, 7.69; N, 14.83; S, 11.47.

***t*-Octylaminomalononitrile (12).**—A 3-g quantity of the methanesulfonic acid salt of **12** was dispersed in 50 cc of ether contained in a separatory funnel. Upon shaking with a concentrated aqueous solution of $KHCO_3$ the salt dissolved completely. The ether layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo*, leaving an almost colorless oil. This oil was diluted with 10 cc of pentane and crystallized almost entirely upon cooling to −10°. Filtration yielded 1.74 g (87%) of **12** as colorless needles, which were stable at −10° but darkened upon standing at room temperature in air: ir (neat) 3380 (m, NH), 2200 cm^{-1} (w, C≡N); nmr (CCl_4) δ 1.01 [9 H, $C(CH_3)_3$], 1.23 [6 H, $C(CH_3)_2$], 1.42 (2 H, CH_2), 1.91 and 2.02 (d, 1 H, J = 10.6 Hz, NH, disappears on deuteration), 4.58 and 4.69 ppm (d, 1 H, J = 10.6 Hz, CH disappears on deuteration); mass spectrum (70 eV) m/e 193 (parent) absent, 178 (parent − CH_3), 122 [parent − $CH_2C(CH_3)_3$].

Anal. Calcd for $C_{11}H_{19}N_3$: C, 68.37; H, 9.88; N, 21.75; mol wt, 193.33. Found: C, 68.12; H, 9.92; N, 21.23; mol wt, 207 (Thermonam, acetone).

4-Cyano-5-*tert*-octylaminoimidazole (14).—The crystalline high-melting by-product obtained in the reaction of TMP with HF and HCN was recrystallized twice from chloroform, using charcoal treatment the first time to give 8.7 g of **14**: mp 195–196°; uv max (methanol) 248 mμ (log ε 4.03); ir ($CHCl_3$) 3430, 3360 (m, NH), 2210 (vs, C≡N), 1620 (s), 1555 (s), 1495 cm^{-1} (m); nmr ($CDCl_3$ + DMSO-d_6) δ 0.81 [9 H, $C(CH_3)_3$], 1.63 [6 H, $C(CH_3)_2$], 1.89 (2 H, CH_2), 4.94 (2 H, NH, disappears upon deuteration), 7.12 ppm (1 H, =CH); mass spectrum (70 eV) m/e parent 220.

Anal. Calcd for $C_{12}H_{21}N_4$: C, 65.40; H, 9.16; N, 25.43. Found: C, 65.14; H, 9.21; N, 25.47.

Compound **14** is easily soluble in dilute (1 *N*) aqueous HCl and may also be purified by filtration of the solution thus obtained, followed by neutralization with a solution of $KHCO_3$. The reprecipitated **14** is collected by filtration, washed with water, and recrystallized from hot chloroform after drying ($MgSO_4$).

When the reaction mixture of TMP with HCN and HF is worked up directly with $KHCO_3$, Et_3N, Et_2NH, or Ph_3P,[18] small amounts of **14** are also among the recovered products.

Registry No.—**1**, 30768-56-0; **1** (CH_3SO_3H), 30768-57-1; **3**, 31819-44-0; **4**, 30768-59-3; **5**, 30768-60-6; **6**, 30768-61-7; **7**, 30768-62-8; **8**, 31819-49-5; **9**, 30768-64-0; **11**, 30826-52-9; **12**, 31819-52-0; **12**

(CH_3SO_3H), 30768-66-2; **14**, 30771-61-0; TMP, 107-40-4; HCN, 74-90-8; HF, 7664-39-3.

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Arylnaphthalene Lignans. Synthesis of Justicidin E, Taiwanin C, Dehydrodimethylconidendrin, and Dehydrodimethylretrodendrin

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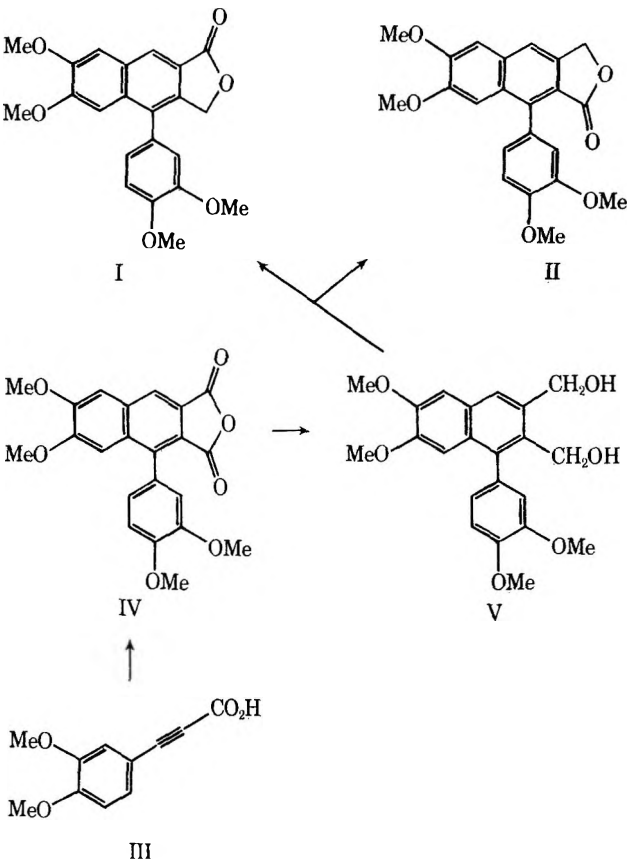
The naturally occurring lactones, justicidin E (VII) and taiwanin C (VI), have been synthesized by a short pathway starting from piperonylpropiolic acid. The tetramethoxy analogs, dehydrodimethylconidendrin (I) and dehydrodimethylretrodendrin (II), have been correspondingly obtained. Application of nmr spectroscopy to the structure elucidation of lignan arylnaphthalene lactones is discussed.

The arylnaphthalene lactones, dehydrodimethylconidendrin (I) and dehydrodimethylretrodendrin (II), although not yet reported to be naturally occurring, have been significant in the development of lignan chemistry, notably in the pioneering work of Haworth. Several interconversions with other classes of lignans have been achieved and syntheses of varying degree of complexity reported.[1-10]

We have sought to examine the generality of our recently reported synthesis[11] of helioxanthin by extension to a short convenient synthesis of dehydrodimethylconidendrin (I). Treatment of 3,4-dimethoxyphenylpropiolic acid (III) with acetic anhydride yielded 6,7-dimethoxy-1-(3′,4′-dimethoxyphenyl)naphthalene-2,3-dicarboxylic acid anhydride (IV),[2,12] which on reduction with lithium aluminum hydride in tetrahydrofuran solution gave the corresponding diol V. Treatment of V with silver carbonate–Celite (Fétizon's reagent)[13] resulted in smooth oxidation to a mixture of the lactones, dehydrodimethylconidendrin (I) and dehydrodimethylretrodendrin (II), in a ratio of approximately 9:1, as indicated by integration of the nmr spectrum of the lactone mixture. The lactone I was readily obtained by direct crystallization and the minor component, the lactone II, was isolated by thin layer chromatography of the crystallization mother liquors.

Although the methylenedioxy analogs VI and VII were first synthesized[14] in 1936 by the multistep procedures developed by Haworth for the tetramethoxy lactones I and II, they have only recently been reported to be of natural occurrence and no direct comparison, other than melting point proximity, has been made. Several crystalline extractives have been isolated[15] from the heartwood of *Taiwania cryptomerioides* Hayata and for one of these, taiwanin C, the structure 6,7-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid lactone (VI) has been proposed.[16] The isomeric structure VII has been proposed for a lactone, justicidin E, isolated as a piscicidal constituent from *Justicia procumbens*, and the conversion of (−)-parabenzlactone (VIII) to justicidin E is indicated in the same communication.[17]



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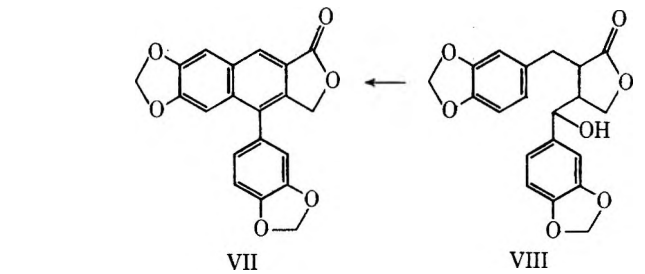
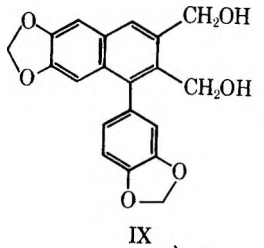
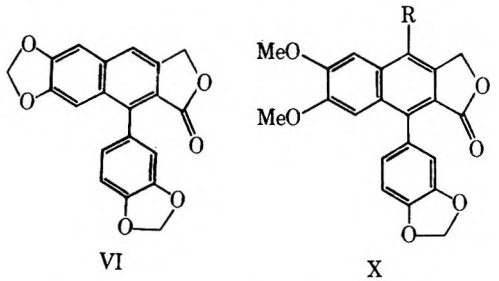
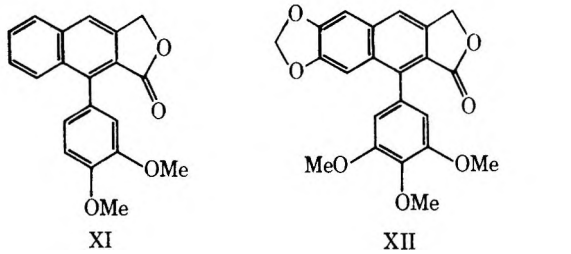
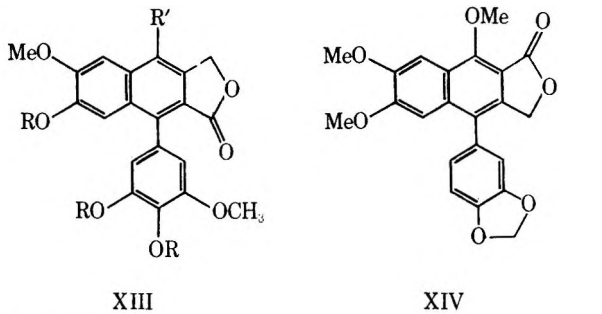
We have now prepared taiwanin C and justicidin E by the same simple pathway used for the tetramethoxy lactone I and II and with constants in excellent agreement with those reported for the natural products. 2,3-Bishydroxymethyl-6,7-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)naphthalene (IX), readily obtained from piperonylpropiolic acid by the action of acetic anhydride followed by reduction with lithium aluminium hydride and aluminium chloride in tetrahydrofuran,[18] was oxidized by silver carbonate–Celite to give a lactone mixture from which the major component, justicidin E (VII), was obtained by direct crystallization and the minor component, taiwanin C (VI), by thin layer chromatographic separation of the mother liquor residue.











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In the structure elucidation of naturally occurring lignan arylnaphthalene lactones, two diagnostic problems have in the past led to erroneous structure assignments. The first concerns whether the γ-lactone function is of the 1-aryl-3-naphthoic acid (*e.g.*, I and VII) or 1-aryl-2-naphthoic acid (*e.g.*, II and VI) types. These can now be clearly differentiated from pmr spectrum examination. A survey of the data available for compounds of established structure, initially by Horii[19] and supplemented herein, indicates that a lactone methylene group of type I, under the shielding influence of the benzenoid C ring, gives in deuteriochloroform solution a signal at δ 5.08–5.23, whereas that of type II is located at δ 5.32–5.54. Corroboration is also available for those lactones possessing a proton at C-4, the signal ascribed to this proton[10] in type I (strongly deshielded by the proximate carbonyl function) being at lower field (δ >8.0, typically at δ *ca.* 8.3) than that of type II (<8.0, typically at δ *ca.* 7.7).

The second problem is concerned with ascertaining, in those arylnaphthalenes possessing the frequently encountered veratrole moiety, whether the methoxyl groups are located in ring A (at C-6 and -7) or ring C (at C-3′ and -4′). The natural lactone, justicidin B (X, R = H),[20–22] has two methoxyl groups (δ 3.80 and 4.30) now known by degradation and synthesis evidence to be in ring A and which can be assigned respectively to C-7 and C-6, the more shielded group being closer to the influence of the aromatic ring C. Since dehydroanhydropicropodophyllin (XII) gives a six-proton signal at δ 3.83 and a three-proton signal at δ 3.96, the former can be attributed to the C-3′ (and -5′) methoxyl group and the latter to the C-4′ methoxyl group;[10] in agreement, the synthetic lactone[10] XI gives methoxyl signals at δ 3.87 (which can now be assigned to C-3′) and δ 3.98 (assigned to C-4′). With this data as an empirical basis for assignment of methoxyl resonance signals, noting particularly that the ring A pair exhibit a chemical shift difference, Δδ 0.23, and the ring C pair difference being Δδ 0.13, assignments could reliably be made for each of the four such functions in compounds I, II, IV, and V. From this background and other data available for arylnaphthalenes of known structure, the diagnostically useful range incorporated in Table I emerges.

Application of this information to the trimethyl ether of plicatinaphthalene (XIII, R = CH_3; R′ = H)[23] permits assignment of the reported methoxyl resonances, *viz.*, δ 4.02 (C-6), 3.77 (C-7), 3.82 (C-3′ and -5′), and 3.94 (C-4′) and to the tetramethyl ether derivative of plicatinaphthol (XIII, R = CH_3; R′ = OCH_3),[24] *viz.*, δ 4.06 (C-6), 3.78 (C-7), 3.84 (C-3′ and -5′), 3.97 (C-4′), and 4.13 (C-4). This value for the 4-methoxyl protons in XIII is in good agree-

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TABLE I

CHEMICAL SHIFT VALUES (δ) IN $CDCl_3$ SOLUTION

	Type I lactone (aryl-3-naphthoic acid)		Type II lactone (aryl-2-naphthoic acid)
Lactone methylene	5.08–5.23		5.32–5.54
H-4	*Ca.* 8.3		*Ca.* 7.7
4-OMe	*Ca.* 4.35		*Ca.* 4.1
Ring A (6,7-dimethoxyl)		Δ 0.21–0.28	
Ring C (3′,4′-dimethoxyl)		Δ 0.10–0.14	

ment with the value (δ 4.09) reported for justicidin A (X, R = OCH_3),[20] another type II lactone, and, in comparison with the values reported for 4-methoxy-substituted type I lactones, justicidin C (δ 4.37) and justicidin D (δ 4.33)[25] provide a further useful distinguishing feature.

Very recently, structure XIV has been proposed[26] for neojusticin B, a lignan isolated from *Justicia procumbens* var. *leucantha*. Evidence used in support of the location of the methylenedioxy group in ring C rather than A, namely the appearance of a mass spectrum fragment (*m/e* 121) characteristic of a methylenedioxyphenyl group, is not totally unequivocal. The reported signals at δ 3.83, 4.05, and 4.37 for three methoxyl groups, however, entirely supports the proposed structure. Thus, by reference to Table I, the last is as expected for a C-4 methoxyl group in a type II lactone, and the chemical shift difference (Δδ 0.22) locates the first two at C-7 and C-6 of ring A.

Experimental Section

Unless otherwise stated, the following generalizations apply. Melting points were determined either with a Gallenkamp or Fisher-Johns apparatus. Nmr spectra (δ) were determined for solutions in deuteriochloroform with tetramethylsilane as internal reference at 60 mc/sec.

Mass spectra were obtained at 70 eV using a AEI MS-12 instrument. Infrared spectra (λ, μ) were determined as KBr disks and ultraviolet spectra (λ, nm) in ethanol solution.

6,7-Dimethoxy-1-(3′,4′-dimethoxyphenyl)naphthalene-2,3-dicarboxylic Acid Anhydride (IV).—3,4-Dimethoxyphenylpropiolic acid (2 g, mp 144–145°) was added to acetic anhydride (10 ml), heated under reflux for 4 hr, and cooled. The tetramethoxy anhydride IV separated as a yellow solid (1.25 g): mp 302° (lit. mp 305–306°,[2] 316–317°[27]); λ 5.46 and 5.63 μ (anhydride); δ 3.84 s (7-OMe), 3.90 s (3′-OMe), 4.00 s (4′-OMe), 4.09 s (6-OMe), 6.93–7.25 complex m (four Ar H), 7.38 s (H-5), and 8.35 s (H-4); *m/e* 394 (M^+).

2,3-Bishydroxymethyl-6,7-dimethoxy-1-(3′,4′-dimethoxyphenyl)naphthalene (V).—The tetramethoxy anhydride (1.2 g) and excess lithium aluminium hydride were heated under reflux in tetrahydrofuran solution overnight and worked up in the usual way and the product was recrystallized from methanol to give the diol V as needles (350 mg): mp 189–190° (lit.[9] mp 188–189°); δ 3.03 br (two OH groups), 3.72 s (7-OMe), 3.83 s (3′-OMe), 3.97 s (4′ and 6-OMe), 4.62 s (C-2 CH_2OH), 4.88 s (C-3 CH_2OH), 6.78 s (H-8), 6.87–6.98 m (three Ar H), 7.13 s (H-5), and 7.68 s (H-4); *m/e* 384 (M^+).

Action of Silver Carbonate–Celite on 2,3-Bishydroxymethyl-6,7-dimethoxy-1-(3′,4′-dimethoxyphenyl)naphthalene (V).—The silver carbonate–Celite reagent (3 g) was added to a solution of the tetramethoxydiol (165 mg) in benzene (50 ml), and the mixture was heated under reflux for 5 hr, after removal of a small volume of solvent by distillation. It was then filtered and washed with ethyl acetate and benzene, and the combined filtrate and washings were evaporated to yield a residual orange gum (137 mg) which solidified upon addition of methanol. Two recrystallizations from this solvent gave 6,7-dimethoxy-1-(3′,4′-dimethoxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid lactone (I) (dehydrodimethylconidendrin) (32 mg) as tiny needles: mp 215–216° (lit.[2] mp 213–215°); λ 5.64 and 5.69 μ (lactone); λ 202 nm (ε 27,500), 224 (21,200), 229 (20,900), 257 (34,300), 319 (8000), and 350 infl (3000); δ 3.83 s (7-OMe), 3.89 s (3′-OMe), 3.99 s (4′-OMe), 4.04 s (6-OMe), 5.23 s (lactone methylene), 6.87–7.07 m (three Ar H), 7.15 s (H-8), 7.32 s (H-5), and 8.31 s (H-4); *m/e* 380 (M^+).

The mother liquors from the above recrystallizations (from two experiments) were combined, taken to dryness, and chromatographed on silica gel PF plates using petroleum ether (bp 38–60°)–ethyl acetate (1:1) with trace of acetic anhydride. The slower running zone (blue fluorescence under uv light) was eluted with ethyl acetate and crystallized once from methanol to give 6,7-dimethoxy-1-(3′,4′-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid lactone (II) (dehydrodimethylretrodendrin) as pale yellow rhombs: mp 253–255° (lit. mp 254–255°,[2] 245–249°,[9] 251.5–253°[10]); λ 5.69 μ (lactone); λ 214 nm (ε 31,800), 221 (31,600), 250 infl (49,700), 258 (59,400), 286 (9200), 311 (10,900), and 346 (5200); δ 3.78 s (7′-OMe), 3.87 s (3′-OMe), 3.97 s (4′-OMe), 4.04 s (6-OMe), 5.37 d (J = 1.2 Hz) (lactone methylene), 6.93–7.03 m (three Ar H), 7.17 s (H-8), 7.20 s (H-5), and 7.72 br s (H-4); *m/e* 380 (M^+). Integration of the nmr spectrum of the crude lactone mixture indicated the 3-carboxylic acid lactone:2-carboxylic acid lactone ratio of *ca.* 9:1.

Action of Silver Carbonate–Celite on 2,3-Bishydroxymethyl-6,7-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)naphthalene (IX).—The silver carbonate–Celite reagent (7 g) was added to a solution of the diol (383 mg) in benzene (150 ml) and the mixture was heated under reflux for 4 hr after removal of a small volume of solvent by distillation. It was then filtered and washed with chloroform, and the combined filtrate and washings were evaporated. The residual solid (308 mg, mp 257–265°) was crystallized three times from chloroform to give analytically pure 6,7-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid lactone (VII) (justicidin E) as needles (90 mg): mp 271–272° (lit. mp 264°,[14] 265–271°[17]); λ 5.69 μ (lactone); λ (methanol) 212 nm (ε 44,100), 223 (28,700), 249 (49,300), 256 (50,800), 299 sh (12,500), 313 (14,000), and 346 sh (5200); δ 5.17 s (lactone methylene), 6.07 s (two methylenedioxy groups), 6.77 m (H-6′, J = 8, 1 Hz), 6.82 (H-2′), 6.98 d (H-5′, J = 8 Hz), 7.10 s (H-8), 7.30 s (H-5), and 8.28 s (H-4); *m/e* 348 (M^+).

Anal. Calcd for $C_{20}H_{12}O_6$: C, 68.96; H, 3.47. Found: C, 68.51; H, 3.40.

The crystallization mother liquors from several such experiments were combined and subjected to preparative thin layer chromatography [1-mm silica gel PF, 20 × 20 cm developed with 1:1 petroleum ether (bp 38–60°)–ethyl acetate with trace of acetic anhydride]. The front running zone (dark blue on ultraviolet irradiation) was mainly justicidin E and the broad slower running zone (light blue on irradiation) was a mixture, eluted from the plates with ethyl acetate and crystallized from chloroform. In this way, the mixture (123 mg) yielded 23.5 mg of 6,7-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid lactone (taiwanin C) (VI) as a microcrystalline powder: mp 272–276.5° (lit. mp 275°,[14] mp 276°[16]); λ 5.67 μ (lactone); λ (methanol) 218 nm (ε 17,700), 222 (18,000), 252 sh (36,100), 258 (38,500), 295 (8400), 304 (8100) and 350 (4300); δ 5.37 br s (lactone methylene), 6.07 s (two methylenedioxy groups), 6.78 m (H-6′, J = 8, 1 Hz), 6.83 (H-2′), 6.98 d (H-5′, J = 8 Hz), 7.13 (H-8), 7.20 (H-5), and 7.69 br s (H-4); *m/e* 348 (M^+).

Inspection of the nmr spectrum of the crude oxidation mixture indicated the lactones were present in an approximate ratio of justicidin E (80%)–taiwanin C (20%).

Registry No.—I, 6258-38-4; II, 6258-39-5; IV, 25936-93-0; V, 31337-51-6; VI, 14944-34-4; VII, 27792-97-8.

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Notes

Lignan Lactones. Synthesis of (≡)-Collinusin and Justicidin B[1]

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There has been considerable activity recently concerning the isolation, structure elucidation, and synthesis of lignan lactones. At least 14 members[2-18] of this group of natural products have known constitutions based on 2, 3-dimethylnaphthalene. In addition, three further natural products,[19-22] which are based on a phenyldihydronaphthalene parent, have recently been described. We report here a synthesis of (≡)-collinusin (I) and justicidin B (II), a representative of each class.

Cleistanthus collinus (Roxb.) Benth. & Hook is a highly poisonous plant which has reputedly been used for insecticidal, piscicidal, and suicidal purposes.[23] From the leaves, Govindachari and coworkers isolated ellagic acid, diphyllin, and two new lactones which were named cleistanthin (a glycoside of diphyllin) and collinusin for which the structure I was proposed.[19,24] The synthesis of this lactone which we have undertaken is in complete support of this structure. The route we have utilized is based on the procedure developed by Klemm and his coworkers for a general synthesis of lignan lactones and demonstrated specifically for γ-apopicropodophyllin and dehydro-β-peltatin methyl ether.[25-27] It appeared that this pathway would be readily adaptable to collinusin; the key step (V → I), however, involving the cyclization of a cinnamyl phenylpropiolate ester to a phenyl dihydronaphthalene lactone was not entirely satisfactory, and the derived product I could only be separated from the reaction mixture with considerable difficulty and loss. The lack of specificity in cyclization may limit the general applicability of this pathway.

The key intermediate was 3, 4-dimethoxycinnamyl 3, 4-methylenedioxyphenylpropiolate (V), conveniently obtained by heating 3,4-methylenedioxyphenylpropiolic acid chloride (III) with 3,4-dimethoxycinnamyl alcohol (IV, R = H). Since the crude ester had infrared and nuclear magnetic resonance spectra in complete accord with structure V, it was used without further purification and heated under reflux with acetic anhydride to effect cyclization. Thin layer chromatographic examination of the product indicated the presence of three principal constituents, of which the fastest running, readily separable from the other two, was identified by comparison with an authentic specimen as 3,4-dimethoxycinnamyl acetate (IV, R = CH_3CO).

Satisfactory separation of the two other components was only achieved by a repetition of the thin layer chromatographic separation and recrystallization. The slower running compound (obtained pure in 9% yield) had constants in accord with the proposed structure, 3,4-dihydro-6,7-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone (I). A direct comparison of the nmr spectra of this synthetic product and natural collinusin confirmed the structure.[28]

(1) (a) The awards of a research grant (AM 13708) from the National Institute of Arthritis and Metabolic Diseases, and Institutional Grant (IN-29) from the American Cancer Society and a Fellowship (to E. B.) from the Gillette Co., are gratefully acknowledged. (b) A preliminary communication outlining this work has appeared: E. Block and R. Stevenson, *Chem. Ind. (London)*, 894 (1970).

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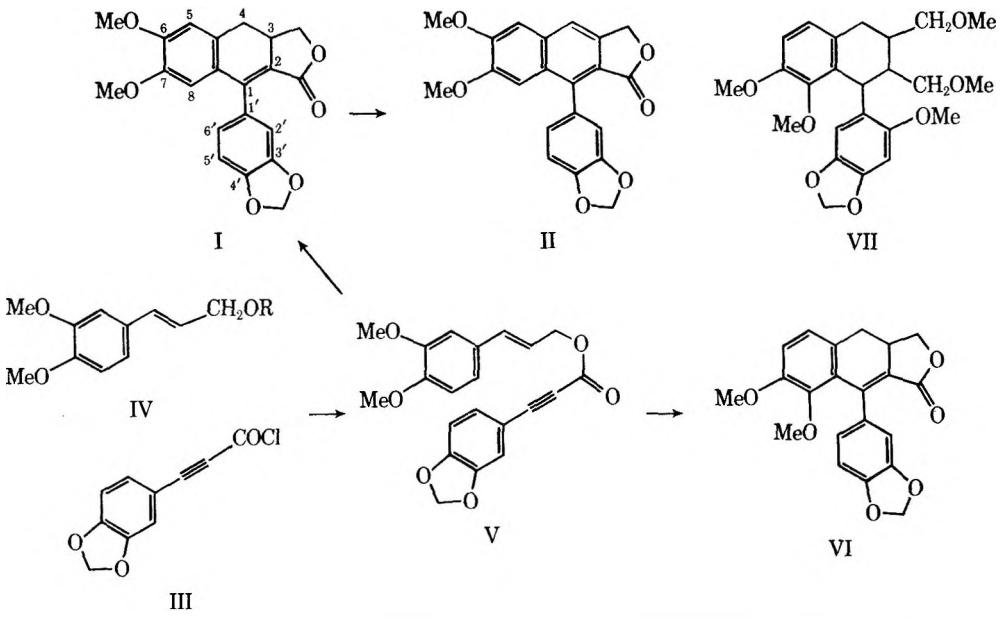

The third product (obtained pure in 5% yield) was isomeric with collinusin and is formulated as 3,4-dihydro-7,8-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone (VI), *i.e.*, the product formed by cyclization ortho to the original 3-methoxyl group rather than para as in the formation of collinusin. Of diagnostic significance in the nmr spectrum, the upfield singlet signal at δ 6.57 of collinusin, attributable to the aromatic H-8 proton being shielded by ring C, is absent and replaced by the signal (δ 3.22) attributable to a shielded methoxyl group attached to C-8. Previous study of the generality of cyclization of substituted *trans*-cinnamylphenylpropiolates[26] indicated that there could be obtained, in addition to the lactone of type I (*i.e.*, 6,7-disubstituted), a product which was probably a molecular compound composed of lactone types I and VI (*i.e.*, 7,8 disubstituted); since, however, efforts to separate the components were unsuccessful, this postulate was deemed tentative and an alternative explanation suggested. In view of the fact that we have now separated (with considerable difficulty) and identified the two pure lactones I and VI, the composite nature of these earlier products is supported. With the establishment of the location of the methoxyl groups at C-7 and C-8 in product VI, it is of interest that the recently revised[29] structure VII for the phenyltetralin lignan, hypophyllanthin, incorporates this same structural feature.

Govindachari and coworkers[19,24] obtained dehydrocollinusin (II) by palladium–carbon dehydrogenation of (+)-collinusin and noted that the physical constants were strikingly close to those reported for justicidin B, a piscicidal extractive isolated by Munakata and coworkers[6,7] from *Justicia Hayatai* var. *decumbens*, although the unavailability of justicidin B precluded a direct comparison. We have now shown that (±)-collinusin is very smoothly oxidized to dehydrocollinusin by the action of *N*-bromosuccinimide. Comparison of the nmr spectrum[28] of our synthetic dehydrocollinusin with that obtained from natural collinusin and now with justicidin B[30,31] establishes the identity. A six-stage synthesis of justicidin B from methyl eugenol oxide in an overall yield of 1–2% has been communicated.[7]

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Experimental Section

Melting points are uncorrected. Infrared spectra (ν) were recorded using a Perkin-Elmer Model 137 spectrophotometer and ultraviolet spectra (λ, nm) with a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra (δ, ppm) were determined for solutions in deuteriochloroform with tetramethylsilane as internal reference at 60 MHz; J values are in hertz.

3,4-Dimethoxycinnamyl Alcohol (IV, R = H).—A solution of methyl 3,4-dimethoxycinnamate[32] (11.1 g) in ether (250 ml) was added to lithium aluminium hydride (3.93 g) in the same solvent (300 ml) at −10 to −15° over 3 hr. Stirring was continued for a further hour and the product worked up in the usual way. Evaporation of the ether extract gave the alcohol as a slightly yellow solid, mp 64–72° (lit.[33] mp 78°), used without further purification; ν (KBr) 3571 cm^{-1} (hydroxyl); δ 2.12 br (OH group), 3.85 s (two OCH_3 groups), 4.28 d (J = 5 Hz, allylic hydroxymethylene group), 5.96–6.72 m (two vinyl protons), and 6.75–7.03 m (three Ar H).

3,4-Methylenedioxyphenylpropiolic Acid Chloride (III).—3,4-Methylenedioxyphenylpropiolic acid[34] (774 mg) was added to an excess of freshly purified thionyl chloride, the mixture stirred at room temperature until solution was complete, and the excess thionyl chloride removed by repeated addition of benzene and evaporation under reduced pressure. The residual acyl chloride had ν ($CHCl_3$) 2203 (C≡C), 1761 and 1736 cm^{-1} (COCl); δ 6.05 s (methylenedioxy group), 6.85 d (J = 8.5 Hz, H-5), 7.03 d (J = 1.3 Hz, H-2), 7.25 q (J = 1.3, 8.5 Hz, H-6).

3,4-Dimethoxycinnamyl 3,4-Methylenedioxyphenylpropiolate (V).—A mixture of acid chloride III (830 mg), 3,4-dimethoxycinnamyl alcohol (801 mg), and pyridine (0.4 ml) in benzene (15 ml) was heated under reflux for 5 hr, cooled, and then washed successively with water, 2 *N* hydrochloric acid, water, saturated sodium carbonate solution, and water. Evaporation of the dried (Na_2SO_4) extract gave the crude ester as an oil (1.57 g): ν ($CHCl_3$) 2225 (C≡C), 1712 (ester), and 965 cm^{-1} (trans alkene); δ 3.83 s and 3.85 s (OCH_3 groups), 5.95 s (methylenedioxy group), 4.84 d (J = 6 Hz, methylene group), and 6.0–7.3 m (aromatic and vinyl protons).

Cyclization of 3,4-Dimethoxycinnamyl 3,4-Methylenedioxy-

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phenylpropiolate.—The crude ester (1.35 g) was dissolved in acetic anhydride (25 ml) and heated under reflux for 11 hr, the solvent removed under reduced pressure, and the residue subjected to thin layer chromatography on silica gel PF (1.0 mm) using ethyl acetate–chloroform (1:9). Two principal zones (R_f 0.46 and 0.53) which overlapped were separated and eluted, and the chromatographic treatment was repeated.

Crystallization of the slower running component from acetone–petroleum ether (bp 60–110°) and then propanol yielded **3,4-dihydro-6,7-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone** [(±)-**collinusin**] (I) as a white solid (121 mg): mp 195–198°; ν (KBr) 1742 (conj γ-lactone), 1626, 1603, 1565, 1502 and 928 cm^{-1}; λ (C_2H_5OH) 248 nm (log ϵ 4.18) and 344 (3.99); δ 3.66 s (C-7 methoxyl), 3.90 s (C-6 methoxyl), 5.98 s (methylenedioxy group), 6.57 s (H-8), 6.80 br (four Ar H), and 2.67–4.82 complex m (5 protons; benzylic, allylic, and lactone methylene protons).

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 68.36; H, 5.17.

Crystallization of the faster running component from methylene chloride–petroleum ether (bp 38–54°) yielded **3,4-dihydro-7,8-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone** (VI) as a white solid (63 mg): mp 213–215°; ν 1748 (conj γ-lactone), 1631, 1542, 1484, and 937 cm^{-1}; λ (C_2H_5OH) 240 nm (log ϵ 4.13) and 295 (4.15); δ 3.22 s (C-8 methoxyl), 3.80 s (C-7 methoxyl), 5.96 s (methylenedioxy group), 6.80–6.95 (five Ar H), and 2.62–5.40 complex m (5 protons, benzylic, allylic, and lactone methylene protons).

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 69.04; H, 5.00.

Elution of a still faster running zone (R_f 0.62) yielded an oil (48 mg) identified as **3,4-dimethoxycinnamyl acetate** (IV, R = $COCH_3$)[35] by comparison with an authentic sample prepared by treatment of 3,4-dimethoxycinnamyl alcohol with acetic anhydride in pyridine. It had ν 1730 (carbonyl) and 966 cm^{-1} (trans alkene); δ 2.08 s (acetate methyl group), 3.87 s and 3.88 s (methoxyl groups), 4.72 d (J = 6 Hz, allylic CH_2), 5.90–6.72 m (two vinyl protons), and 6.77–7.12 m (three Ar H).

Conversion of (±)-Collinusin to Justicidin B.—A mixture of collinusin (25.5 mg), *N*-bromosuccinimide (15 mg), and benzoyl peroxide (2 mg) in carbon tetrachloride (20 ml) was heated under reflux for 10 min during which time the solution turned yellow and then for a further 20 min after which time the color had been discharged. The cooled and filtered solution was evaporated under reduced pressure and the residue chromatographed on a silica gel PF plate (1.0 mm) with ethyl acetate–chloroform (1:9). Elution of the zone R_f 0.31 yielded a product (24 mg) which on crystallization from acetone–ether gave **6,7-dimethoxy-3-hydroxymethyl-1-(3′,4′-methylenedioxyphenyl)naphthalene-2-carboxylic acid lactone** (**justicidin** B) (II) as needles: mp 237–238° (lit.[31] mp 240°); ν (KBr) 1761 (lactone), 1623 and 933 cm^{-1}; λ ($CHCl_3$) 260 nm (log ϵ 4.77), 296 (4.02), 308 (4.02), and 350 (3.73); δ 3.80 s (C-7 methoxyl), 4.03 s (C-6 methoxyl), 5.37 d (J = 1 Hz, lactone methylene), 6.00 d and 6.07 d (J = 1.5 Hz, methylenedioxy group), and 6.75–7.70 (five Ar H).

Registry No.—I, 28982-10-7; II, 17951-19-8; III, 31337-55-0; IV (R = H), 18523-76-7; IV (R = $COCH_3$), 31337-58-3; V, 28908-38-5; VI, 31337-60-7.

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Base-Catalyzed Rearrangement of ω-Bromolongifolene

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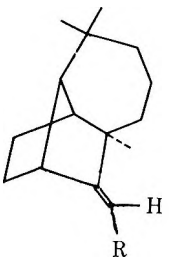
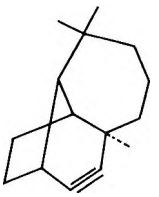
We wish to report here the generation and capture of a highly strained tricycloalkyne,[1] the 3,8,8-trimethyltricyclo[7.3.0.0^{4,10}]dodec-2-yne (**3**) (longifolyne), *via* a base-induced Fritsch–Buttenberg–Wiechell rearrangement[2] of ω-bromolongifolene (**2**). Bhattacharyya and coworkers[3] have recently reported that fusion of **2** with potassium hydroxide at 400° gave a mixture of ring-expanded ketones, longihomocamphenilone (**4**) and longiisohomocamphenilone (**5**), in 5–7% yield together with a dimeric dilongifolenyl ether (**6**). The nature of the ring enlargement products was suggestive of the possible intermediacy of cycloalkyne **3** in the alkali fusion reaction. The intervention of **3** in the rearrangement of ω-bromolongifolene with potassium *tert*-butoxide is described here.



1, R = H
2, R = Br



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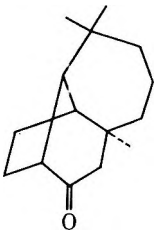

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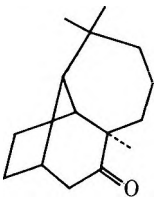

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Longifolene (**1**) was converted into ω-bromolongifolene (**2**) in one step *via* vinylic bromination with *N*-bromosuccinimide in refluxing benzene. The diagonistic feature of the nmr spectrum was the appearance of the olefinic proton singlet at τ 4.37 and an allylic bridgehead proton signal at τ 6.87 [*cf.* longifolene (**1**) at τ 7.42]. The strong deshielding[4] of the allylic bridgehead proton leads to assignment of bromine as anti with respect to the large ring. This is in conformity with the X-ray crystal structure[5] of **2**. On refluxing with potassium *tert*-butoxide in toluene the ω-bromomethylene derivative **2** readily rearranged to cycloalkyne **3** and was trapped with 1,3-diphenylisobenzofuran to furnish an adduct, mp 254–256°, in 85% yield. The adduct is devoid of any olefinic proton absorption in the nmr spectrum but exhibits signals at τ 9.11, 9.30, and 9.51 (3 H, s, Me), 7.25 (1 H, broad, allylic bridgehead), and 1.8–1.3 (14 H, m, aromatic) leading to its formulation as **7**. The endo geometry of the ether bridge in **7** is deduced from the steric considerations as well as exceptional shielding (τ 9.51) of the C_8-methyl group due to the diamagnetic anisotropy of the phenyl ring. The acetylene **3** could also be trapped with tetracyclone **8** to

(1) (a) A. Krebs in "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, p 987; (b) R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967, p 317.

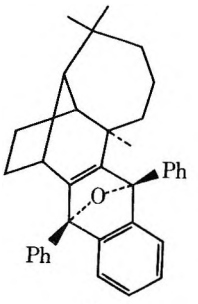
(2) G. Kobrich, *Angew. Chem. Int. Ed. Engl.*, 49 (1965); G. Kobrich and P. Buck, ref 1b, p 99.

(3) M. M. Mehra, B. B. Ghatge, and S. C. Bhattacharyya, *Tetrahedron*, **21**, 637 (1965).

(4) U. R. Nayak, T. S. S. Krishnan, and S. Dev, *ibid.*, **19**, 2281 (1963); S. Ranganathan, A. Goel, and B. B. Singh, *Tetrahedron Lett.*, 3299 (1968).

(5) Private communication from Professor G. Ourisson. We wish to thank Professor Ourisson for this information and a sample of ω-bromolongifolene.

furnish an adduct which after the loss of carbon monoxide gave **9**, mp 261–262°, in 90% yield. The reaction of



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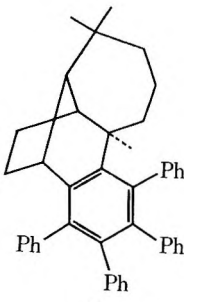
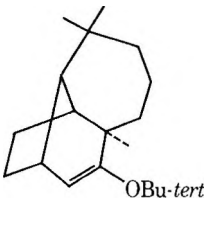


9

ω-bromolongifolene (**2**) with potassium *tert*-butoxide in the absence of any trapping agent furnished a high yield of a mixture containing ketones **4** and **5** and the *tert*-butyl enol ethers **10** and **11**. The formation of

10



11

these compounds is compatible with the formation of **3**. No dimeric products as reported[3] earlier were encountered in this reaction. Mechanistically, this base-induced rearrangement can be visualized as proceeding either *via* an alkylidene carbene[6] or an α-halogenoorganometallic intermediate.[2]

Experimental Section[7]

ω-Bromolongifolene[8] (2).—A solution of longifolene (**1**) (20.4 g, 0.1 mol) and *N*-bromosuccinimide (18 g, 0.1 mol) in dry benzene (150 ml) was refluxed for 4 hr in the presence of a catalytic amount of benzoyl peroxide (100 mg). The reaction mixture was poured into water and the organic layer was successively washed with dilute HCl (10%, three 50-ml portions, saturared $NaHCO_3$ (two 40-ml portions), and brine (two 25-ml portions) and dried. Removal of solvent and distillation gave ω-bromolongifolene: 20 g (72%); mp 40–41°; ir (neat) 3010, 1640, 790 cm^{-1} (>C=C<^{H}); nmr τ 9.04 (6 H, s, gem Me), 8.95 (3 H, s, Me), 4.37 (1 H, s, olefinic), 6.87 (1 H, broad, allylic bridgehead).

Diphenylisobenzofuran Adduct 7 of Acetylene 3.—A mixture of ω-bromologifolene (**3**) (2.8 g, 0.01 mol), potassium *tert*-butoxide (2.16, 0.2 mol), and diphenylisobenzofuran (**6**) (2.7 g, 0.1 mol) was refluxed in dry toluene for 8 hr. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (two 50-ml portions). The organic phase was washed with brine and freed of solvent to give a solid residue, 4.5 g, mp 249–255°. Recrystallization from methanol gave colorless needles: mp 254–256°; ir spectrum 1655, 1603, 701, 690 (aromatic), 1210 cm^{-1} (ether). *Anal.* Calcd for $C_{35}H_{36}O$: C, 88.94; H, 7.68. Found: C, 88.73; H, 7.61.

Tetracyclone Adduct 9 of Acetylene 3.—A mixture of ω-bromolongifolene (2.80 g, 0.1 mol), tetracyclone (3.84, 0.1 mol), and potassium *tert*-butoxide (2.16 g, 0.2 mol) was refluxed in toluene until the color of tetracyclone was completely discharged (6 hr). The reaction mixture was poured into water and extracted with CH_2Cl_2 (two 60-ml portions). Removal of solvent gave a solid residue. Recrystallization from MeOH–C_6H_6 gave colorless crystals: mp 260–262° (90% yield); ir spectrum 695, 1480, 1601 and 3080 cm^{-1}. *Anal.* Calcd for $C_{43}H_{42}$: C, 92.42; H, 7.58. Found: C, 92.13; H, 7.51.

Rearrangement of 2 with Potassium *tert*-Butoxide.—A mixture of ω-bromolongifolene (5.6 g, 0.2 mol) and potassium *tert*-butoxide (7.3 g, 0.4 mol) in toluene was refluxed for 6 hr. The reaction mixture was poured into water and extracted with pentane (three 50-ml portions), washed with brine, dried, and freed of solvent to yield a pale yellow liquid, 4.13 g. A vpc analysis of the product showed the presence of at least seven components. The major components were in the ratio[10] of 1:5:1:2 and were identified as longihomocamphenilone[3,11] (**4**, mp 55–56°), longiisohomocamphenolone[3] (**5**, mp 51–52°), *tert*-butyl enol ether **10** [bp 140–150° (1 mm); ir spectrum 1645, 1170, 1195, 1240 cm^{-1} (enol ether). *Anal.* Calcd for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.21; H, 11.51], and the isomeric *tert*-butyl enol ether **11** [bp 140–145° (1 mm); ir spectrum 1650, 1170, 1190, 1240 cm^{-1} (enol ether). *Anal.* Calcd for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.31; H, 11.59]. The two *tert*-butyl enol ethers were characterized by converting them into the 2,4-dinitrophenylhydrazones of the corrsponding ketones **4**, mp 144°, and **5**, mp 164–165°, by reaction with Brady[12] reagent.

Registry No.—**2**, 1139-15-7; **4** 2,4-DNP, 1607-92-7; **5** 2,4-DNP, 1174-81-8; **7**, 31024-76-7; **9**, 31024-77-8; **10**, 31024-78-9; **11**, 31024-79-0.

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

(7) Melting points and boiling points are uncorrected. All solvent extracts were dried over anhydrous Na_2SO_4. Ir spectra were recorded on a Perkin-Elmer Model 137 infracord as neat liquids or solids as KBr disks. Nmr spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ and chemical shifts are reported on a τ scale relative to tetramethylsilane (τ 10).

(8) The reported[9] preparation of **2** involved a two-step bromination–dehydrobromination of longifolene (**1**) and is less convenient.

(9) G. Dupont, R. Dulon, P. Naffa, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1075 (1954).

(10) The relative amount of the components varied in every reaction with time and the sample of the base used.

(11) P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1115 (1954).

(12) O. L. Brady, *J. Chem. Soc.*, 756 (1931); J. Wolinsky, *J. Org. Chem.*, **26**, 705 (1961).

The Chemistry of Actinobolin. Oxidation of Actinobolamine

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Received January 8, 1971

Aromatization of cyclic portions of actinobolin[2,3] and of the products isolated after base-catalyzed[4,5] hydrolysis of the antibiotic made secure the molecular structures assigned to these compounds. Actinobolamine (**1a**),[5] the product formed by vigorous acid hydrolysis of actinobolin, resisted all attempts at achieving clean eliminative scission of the bond linking C-5 to nitrogen and subsequent aromatization of the substituted cyclohexenone. *N*-Acetylactinobolamine (**1b**) did, however, submit to nitric acid oxidation affording a readily isolable product displaying ir bands characteristic of lactone carbonyl. This observation

(1) (a) Support of this work by the National Institutes of Health through Research Grant AI-04720 is gratefully acknowledged. (b) This paper is based in part on the Ph.D. dissertation of D. B. Nelson. Arizona State University. (c) Presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 014.

(2) M. E. Munk, D. B. Nelson, F. J. Antosz, D. L. Herald, Jr., and T. H. Haskell, *J. Amer. Chem. Soc.*, **90**, 1087 (1968).

(3) F. J. Antosz, D. B. Nelson, D. L. Herald, Jr., and M. E. Munk, *ibid.*, **92**, 4933 (1970).

(4) D. B. Nelson, M. E. Munk, K. B. Gash, and D. L. Herald, Jr., *J. Org. Chem.*, **34**, 3800 (1969).

(5) D. B. Nelson and M. E. Munk, *ibid.*, **35**, 3832 (1970).

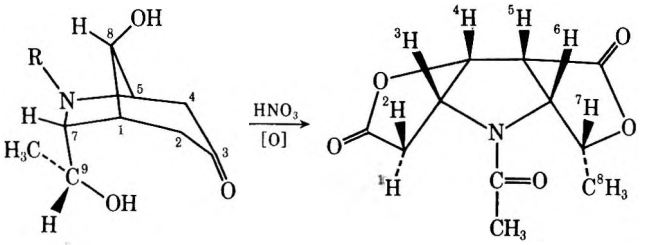
TABLE I

NMR ASSIGNMENTS FOR COMPOUND 2[a,b]

Assignment	Chemical shift[c] (no. of hydrogens)	Multiplicity	Spin decoupling[d] Signal irradiated	Spin decoupling[d] Multiplicity change to
H-8	1.01 (3)	d, $J_{8,7}$ = 6.5 Hz		
N-$COCH_3$	1.93 (3)	s		
H-1	2.67 (1)	d of d, $J_{1,2}$ = 18.5, $J_{1,3}$ = 1.5 Hz	H-3[e]	d, J = 18.5 Hz
H-2	3.07 (1)	d of d, $J_{2,1}$ = 18.5, $J_{2,3}$ = 7.0 Hz	H-3	d, J = 18.5 Hz
H-5	3.70 (1)	d of d, $J_{5,6}$ = 10, $J_{5,4}$ = 7.0 Hz		
H-3	4.73 (1)	Overlapping		
H-7	4.83 (1)	multiplets[f]	H-8	d, J = 8.0 Hz
H-6	4.99 (1)	d of d, $J_{6,7}$ = 8.0, $J_{6,5}$ = 10.0 Hz	H-5	d, J = 8.0 Hz
H-4	5.21 (1)	d of d, $J_{4,3}$ = 5.5, $J_{4,5}$ = 7.0 Hz	H-5	d, J = 5.5 Hz

[a] In DMSO-d_6 at 100°. [b] Addition of D_2O to the nmr sample results in no loss of integral amplitude. [c] In δ units (ppm) downfield of external HMDS. [d] Frequency-sweep spin decoupling at 100 MHz and 100°. [e] Observation of the H-4 signal while irradiating H-3 indicated coupling of H-4 to H-3; however, decoupling of H-4 to a clean doublet, J = 7.0 Hz, was not achieved. [f] Irradiation of H-8 reduces H-7 to a doublet (J = 8.0 Hz) and reveals the H-3 signal as a seven-line pattern compatible with $J_{3,1}$ = 1.5, $J_{3,2}$ = 7.0, and $J_{3,4}$ = 5.5 Hz

suggested an alternate degradation of **1b**, retaining the pyrrolidine ring intact, and led to the studies reported here.



1a, R = H
b, R = CH_3CO

2

Elemental analysis and a mass spectral determination provided a molecular formula of $C_{11}H_{13}NO_5$ for the oxidation product. The infrared spectrum (KBr) displayed prominent bands characteristic of the γ-lactone carbonyl at 1788 and 1768 cm^{-1} together with a tertiary amide carbonyl band at 1640^{-1}. Bands associated with O–H or N–H stretching or indicative of unstrained carbonyl were not observed.

Several oxidative sequences are available to **1b**; however, the presence of two γ-lactone carbonyls in the isolated product and the change in molecular formula, *i.e.*, eq 1, suggest that the oxidation product is formed

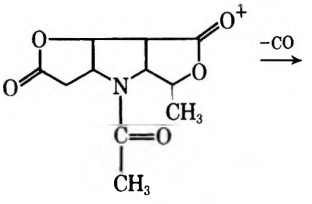
$$C_{11}N_{17}NO_4 \xrightarrow[-2H_2O]{+3O} C_{11}H_{13}NO_5 \qquad (1)$$

by oxidative cleavage of the σ bond linking C-2–C-3 to yield a dicarboxylic acid. Subsequent lactonization, which likely accounts for resistance to further oxidation, gives rise to the di-γ-lactone **2**.

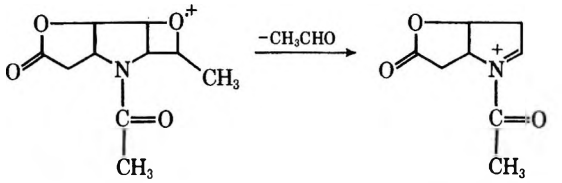
Of the diverse products possible on nitric acid oxidation of **1b** (by oxidation at C-8 and/or C-9 and subsequent σ-bond cleavage or oxidative cleavage about the C-3 ketone) only the di-γ-lactone structure **2** is consistent with the appearance of infrared bands at 1788 and 1768 cm^{-1}. Evidence to secure this structural assignment derives from the 100-MHz spectrum taken at 100° [6] (Table I).

In **1b**, carbon atoms 1, 5, 7, 8, and 9 possess the *R* configuration.[5] Retention of the *R* configuration at the corresponding centers of **2** requires the exo orientation for H-3, H-4, H-5, H-6, and H-7. Dreiding stereomodels indicate that the dihedral angles between each vicinal pair of hydrogens in the series H-3 through H-7 are comparable and small (approaching 0°). In view of the possible influence of the electronegative heteroatom and the electron-withdrawing carbonyl group,[7] the coupling constants observed, $J_{3,4}$ = 5.5, $J_{4,5}$ = 7.0, $J_{5,6}$ = 10.0, and $J_{6,7}$ = 8.0 Hz, while varied, do meet the requirements imposed by the retention in **2** of the stereochemistry assigned to **1b**.

The mass spectrum (see Experimental Section) displays few major peaks, all of which may be explained in terms of structure **2**. Transformation of the parent



a, *m/e* 239



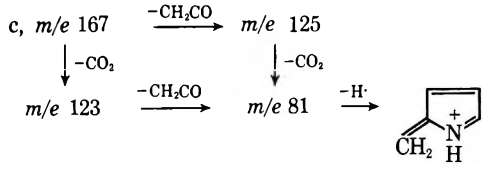
b, *m/e* 211 c, *m/e* 167

(6) Nmr spectra of **2** at room temperature appear to contain two duplicate sets of signals offset slightly from one another. At temperatures greater than 70° these patterns coalesce to a single set of signals. The temperature dependence of the nmr spectrum of **2** is explicable in terms of the presence of two slowly interconvertible rotational isomers which exist by virtue of the limited free rotation imposed by the double bond character of the amide carbon–nitrogen bond.

(7) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 49–54.

ion a (*m/e* 239) to the base ion c (*m/e* 167) can be pictured as proceeding *via* loss of carbon monoxide to b, followed by loss of acetaldehyde to give c. The presence of metastable ions at *m/e* 186.3 and 132.2 support this sequence. The high-resolution mass spectrum of 2 shows the *m/e* 167 peak to be *m/e* 167.0583 (calcd for $C_8H_9NO_3$, 167.0582); therefore, it does not arise *via* loss of carbon monoxide and carbon dioxide from the parent ion.

The pathways followed in the further decomposition of ion c are sequential variations of a common theme, *i.e.*, decay to the resonance stabilized ion d. The



d, *m/e* 80

m/e 125 ion also proceeds to d by the loss of 45 mass units in a sequence which must involve a one-hydrogen transfer prior to loss of a carboxyl radical. The sequences of decay to ion d are supported by the observation of the required metastable peaks.

Experimental Section[8]

Oxidation of *N*-Acetylactinobolamine.[9]—To a prewarmed 50-ml solution of 8 *N* nitric acid was added 2.339 g (10.3 mmol) of *N*-acetylactinobolamine. The exothermic nature of the reaction rapidly brought the solution to a condition of slow reflux which was maintained for a period of 10 min.[10] The reaction solution was poured into 250 ml of chilled water which was passed onto a column containing 550 ml of chilled Bio-Rad AG 21-K anion-exchange resin (hydroxide form). The column was eluted with 500 ml of water and 1500 ml of acetic acid–water (1:9). The eluents were freeze-dried. The bulk of the material appeared in the first 1000 ml of acetic acid eluent as a tan semisolid which on crystallization from ethyl alcohol gave 734 mg of crude **2**. Recrystallization from ethyl alcohol gave 490 mg of **2** as analytically pure material: mp 241° dec; $[\alpha]^{25}D$ +166° (c 6.1%, DMSO); homogenous to tlc (Bio-Sil A,[11a] ethyl acetate–ethyl alcohol, 2:1 v/v, and MN-cellulose,[11b] *n*-butyl alcohol–water–acetic acid, 4:1:5 v/v/v, upper phase). Column chromatography of the crystallization mother liquids (silicic acid[12] eluted with ethyl acetate containing increasing amounts of ethyl alcohol) followed by crystallization from ethyl alcohol gave an additional 155 mg of **2**, mp 241° dec, for a total yield of 645 mg of **2** (2.70 mmol, 26.2%). Pertinent ir and nmr are listed in the text; mass spectrum *m/e* (relative intensity 239 (4), 211 (5), 167 (100), 125 (14), 123 (3), 81 (8), 80 (10), metastable ions at 186.3, 132.2, 93.6, 90.5, 53.3, 52.5, 51.2, 79.0.

Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; O, 33.44; mol wt, 239.0794. Found: C, 55.48; H, 5.71; O, 33.37; mol wt, 239.0807 (mass spectrum).

(8) Instruments used: Thomas-Hoover capillary melting point apparatus (melting points corrected); Perkin-Elmer Model 237B Infracord spectrometer; Rudolf Model 80 polarimeter; Varian Associates HA-100 spectrometer; Atlas CH-4B mass spectrometer (heated inlet, 19 μA, 70 eV); Atlas SM-1B high-resolution mass spectrometer. Fragmentation sequences and metastable peaks were matched with computer program CMSPXS, written by S. H. Brown of Stanford University. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

(9) Performed with Mr. Chidambar L. Kulkarni.

(10) A preliminary thin layer (Bio-Sil A,[11a] ethyl acetate–ethyl alcohol, 2:1 v/v) chromatographic assay of the fate of *N*-acetylactinobolamine (**1b**) and **2** in refluxing nitric acid demonstrated the need for a short contact time.

(11) (a) Bio-Sil A, 10–30 μ with 5% binder, purchased from Bio-Rad Laboratories, Richmond, Calif.; (b) MN-cellulose powder 300G distributed by Brinkman Instruments, Great Neck, N. Y.

(12) Bio-Sil A, 100–200 mesh, purchased from Bio-Rad Laboratories.

Registry No.—**1b**, 31729-81-4; **2**, 31729-82-5.

Acknowledgments.—Special thanks are due to Dr. T. H. Haskell of Parke, Davis and Co., who performed the initial nitric acid oxidation of *N*-acetylactinobolamine, to Professor J. Kutney, University of British Columbia, and W. C. Jankowski, Varian Associates, for nmr spectra, and to Professor P. Brown, Arizona State University, for helpful discussions of the mass spectra. We are indebted to the National Science Foundation for funds to purchase the Atlas CH-4B (Grant GB 4939) and Atlas SM-1B (NSF Grant No. GP-6979).

Polarity Effects in the Solvolysis of Steroid Derivatives. The Synthesis and Acetolysis of 6α-Tosyloxy-3α- and -3β-chloro-5α-cholestane[1]

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Transmission of electrical effects from remote dipolar substituents to a reaction site has been long under investigation.[3] The phenomenon is usually regarded as a manifestation of either an inductive effect operative through the bonds or a field effect operative through space or solvent. In an elegant study of the dissociation constants of 4-substituted bicyclo[2.2.2]octane- and bicyclo[2.2.1]heptane-1-carboxylic acids, Wilcox and Leung[3] found that the ΔpK_a's were best correlated by the field effect model. Recently we reported studies on the influence of polar substituents upon the rate of solvolysis of esters of substituted cyclohexanols[4] and *trans*-1-decalols.[5] In all cases investigated we found that the solvolysis rates are most satisfactorily explained on the basis of a field effect. In this connection it became of interest to us to extend these studies to other conformationally rigid molecules. Because of its established conformational integrity, the steroid nucleus seemed well suited for our purpose. To this end we wish to report the synthesis and acetolysis of the *p*-toluenesulfonate esters of 3α-chloro-5α-chloestan-6α-ol (**4b**) and 3β-chloro-5α-cholestan-6α-ol (**2b**).

Synthetic Method.—Synthetic routes are summarized in Scheme I. Entry into the desired cholestan-6α-ol systems was accomplished smoothly *via* oxidative hydroboration of an appropriate cholesteryl derivative using a modification of the method reported by Shoppee, *et al.*[6] The expected least highly substituted alcohols were obtained in good yield. Stereochemically, the stanol products were exclusively equatorial (6α). This is presumably a result of steric hindrance by the

(1) This research was supported in part by Research Grant GP-6133X from the National Science Foundation.

(2) Postdoctoral Research Associate, 1966–1967. Lecturer in chemistry, 1967–1968.

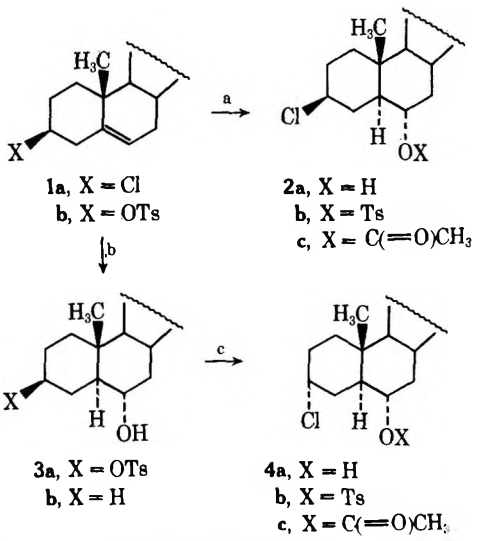
(3) C. F. Wilcox and C. Leung, *J. Amer. Chem. Soc.*, **90**, 336 (1968), and references therein.

(4) D. S. Noyce, B. N. Bastian, P. T. S. Lau, R. S. Monson, and B. Weinstein, *J. Org. Chem.*, **34**, 1247 (1969).

(5) D. S. Noyce and B. E. Johnston, *ibid.*, **34**, 1252 (1969).

(6) C. W. Shoppee, R. Lack, and B. McLean, *J. Chem. Soc.*, 4996 (1964).

SCHEME I[a]



[a] a, X = Cl, B_2H_6, NaOH, 30% H_2O_2; b, X = OTs, B_2H_6, 30% H_2O_2; c, X = OTs, $Et_4N^+Cl^-$, K_2CO_3, DMF.

19-angular methyl group to the diborane approach on the β side of the molecule. Thus **2a** was obtained directly by hydroboration of **1a**.

The synthesis of **4a** by an indirect route (eight steps from cholesterol) has been reported.[6] In addition to low yield, **4a** (and **4c**) could not be induced to crystallize due to contamination. We were able to prepare crystalline **4a** from cholesterol in three steps by taking advantage of the fact that cholestanyl tosylates undergo bimolecular nucleophilic displacement with inversion when treated with chloride ion in refluxing DMF.[7] Treatment of 3β-tosyloxy-5α-cholestan-6α-ol (**3a**) with excess tetraethylammonium chloride in refluxing DMF containing 1 equiv of potassium carbonate gave **4a** in 65% yield.

The *p*-toluenesulfonates of **2a** and **4a** were prepared by standard methods. The conformational assignments of the epimeric chlorides are based upon the synthetic design and are supported by the observation that the carbon–chlorine infrared stretching frequencies are in agreement with those reported earlier.[6]

Kinetic Results.—The first-order rate constants for the acetolyses are summarized in Table I, with the derived thermodynamic parameters in Table II. The acetolysis rate of the unsubstituted 6α-tosyloxy-5α-cholestane (**3b**-OTs) has been reported elsewhere[8] and is also listed in Table I.

TABLE I

RATES OF ACETOLYSIS OF 3-SUBSTITUTED 6α-TOSYLOXY-5α-CHOLESTANES

Compd	Concn of sulfonate, M[a]	Temp,[b] °C	10^5k, sec^{-1}
2b	0.002	75.00	0.343 ± 0.018
	0.002	90.00	2.08 ± 0.05
	0.002	110.00	18.5 ± 0.60
4b	0.002	75.00	0.616 ± 0.012
	0.002	90.00	3.49 ± 0.13
	0.002	110.00	28.6 ± 1.2
3b-OTs[c]	0.01	75.00	2.25 ± 0.02

[a] All solvolyses were carried out in acetic acid with added acetic anhydride and sodium acetate, both at twice the concentration of the sulfonate. [b] Temperatures all within ±0.05°. [c] Reference 8.

TABLE II

ACTIVATION PARAMETERS

Compd	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
2b	29.5 ± 0.2	0.8 ± 0.4
4b	28.3 ± 0.2	−1.3 ± 0.4

The rates of solvolysis in the present study are lower than for the parent compound **3b**-OTs by a factor of four- to sevenfold as is expected for molecules bearing electron-withdrawing substituents. More important are the relative rates for the isomeric compounds. Compound **4b** is the more reactive; at 75.00° k_{4b}/k_{2b} is 1.8, and at 110° it is 1.54. The observed ratios show that there is a significant difference in the solvolysis rates due to the change in orientation of the substituent dipole. As in the earlier studies,[4,5] these results are consistent with the field effect model in that the more reactive epimer **4b** is the one in which the negative end of the dipolar substituent lies closer to the reaction center. The data cannot be explained solely on the basis of an inductive effect, since that model is insensitive to changes in orientation of a dipole at a given position.

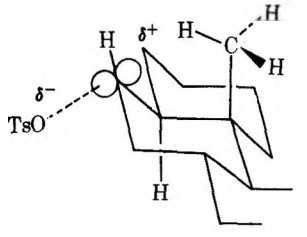
Product Study.—The acetolysis products are listed in Table III. Although excess inversion is usually observed in the substitution products,[4,9] it should be noted that the acetates **2c** and **4c** are exclusively those of retained stereochemistry. Upon inspection it appears that the stereochemistry of the products reflects the steric environment of the incipient carbonium ions. The β side of the developing p orbital of the cation (structure I) is precluded from significant solvation due to shielding by the 19-angular methyl group. On the other hand, the α side of the cation is relatively unhindered, enabling solvent to either capture it (affording **2c** or **4c**) or allowing solvent to remove the 5α proton (producing olefin).

TABLE III

PRODUCTS FROM THE ACETOLYSIS OF 6α-TOSYLOXY-3α- AND -3β-CHLORO-5α-CHOLESTANE

Compd solvolyzed	Products formed,[a] mol % A	B	C	D
2b	51.5	48.5	N.D.[b]	N.D.
4b	25.3	53.1	21.6	N.D.

[a] Products formed: A = 5-ene; B = 6α-acetate; C = 6α-alcohol; D = 6β-acetate. Relative yields reported; total recovery *ca.* 96%. [b] N.D. = none detected.



I

Formation of the 6α-stanol **4a** is probably the result of ester hydrolysis during the work-up or chromato-

(7) G. A. Selter and K. D. Mc Michael, *J. Org. Chem.*, **32**, 2546 (1967).

(8) S. Nishida, *J. Amer. Chem. Soc.*, **82**, 4290 (1960).

(9) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc., B*, 355 (1968).

graphic separation. This conclusion is supported by the fact that no alcohols were detected in the solvolysis products of **2b** even though the same solvent was used in each case.

Experimental Section[10]

3β-Chloro-5α-cholestan-6α-ol (2a).—To a solution of cholesteryl chloride[11] (**1a**) (24.3 g, 60 mmol) in 300 ml of THF was added sodium borohydride (10 g). The mixture was cooled to 0° and stirred under nitrogen as a solution of boron trifluoride etherate (50 ml) in THF (50 ml) was added dropwise over 45 min. After stirring at 25° for 12 hr, the mixture was cooled to 0° and 100 ml of 12% NaOH was added cautiously during 1 hr followed by 75 ml of 30% hydrogen peroxide over 20 min. The mixture was stirred at 25° for 1 hr, diluted with water, and extracted with ether (two times). The combined ether extracts were washed with water (two times), 5% $NaHSO_3$ (two times), and water, dried ($MgSO_4$), and filtered. Ether evaporation under reduced pressure gave a colorless syrup which crystallized from aqueous acetone containing methanol. Three crystallizations from aqueous acetone gave 11.2 g (40%) of the stanol **2a**: mp 101–102° and 110–110.5°; $[\alpha]^{23}D$ +50° (lit.[6] mp 116–118°; $[\alpha]^{23}D$ +52°); ir (CS_2) 3625 (OH), 758 cm^{-1} (equatorial CCl). Treatment of **2a** with acetic anhydride afforded the acetate **2c** which crystallized from acetone–methanol (1:1), mp 97–99°, $[\alpha]^{23}D$ +59° (lit.[6,12] mp 97–99°).

6α-Tosyloxy-3β-chloro-5α-cholestane (2b) was prepared in 97% yield from **2a** in the usual manner. Two crystallizations from acetone gave pure material: mp 162.5–163°; $[\alpha]^{23}D$ +54°; ir (CS_2) 1180 and 1165 (sym S=O), 758 cm^{-1} (equatorial CCl).

Anal. Calcd for $C_{34}H_{53}ClO_3S$: C, 70.73; H, 9.25; Cl, 6.14. Found: C, 70.79; H, 9.40; Cl, 6.25.

3β-Toyloxy-5α-cholestan-6α-ol (3a).—Cholesteryl tosylate[13] (**1b**) (81.1 g, 150 mmol) in THF (700 ml) was hydroborated with sodium borohydride (10 g) and boron trifluoride etherate (30 ml in 25 ml of THF) according to the procedure for **2a**. Subsequent treatment with 12% NaOH (100 ml) and 30% hydrogen peroxide (50 ml) followed by the usual work-up and crystallization from ethanol afforded **3a** (64.7 g, 80%) as colorless crystals: mp 135–135.3°; $[\alpha]^{23}D$ +23°; ir ($CHCl_3$) 3625 (OH), 1188 and 1175 cm^{-1} (sym S=O).

Anal. Calcd for $C_{34}H_{54}O_4S$: C, 73.07; H, 9.73; S, 5.73. Found: C, 72.76; H, 9.96; S, 5.74.

3α-Chloro-5α-cholestan-6α-ol.—A mixture of **3a** (560 mg, 1 mmol), tetraethylammonium chloride (331 mg, 2 mmol), and potassium carbonate (138 mg, 1 mmol) in 30 ml of DMF was refluxed for 25 min. After cooling to 25°, water was added and a white solid was obtained upon additional cooling to 0°. The solid was taken up in ether and filtered to remove the inorganic salts, and the ether was evaporated to give a colorless syrup which was crystallized twice from methanol affording 275 mg (65%) of the stanol **4a**: mp 156–157°; $[\alpha]^{23}D$ +36°; ir (CS_2) 3625 (OH), 720 cm^{-1} (axial CCl). Treatment of **4a** with acetic anhydride gave the acetate **4c**, which crystallized from methanol: mp 100–100.8°; $[\alpha]^{23}D$ +45°; ir (CS_2) 1735 (ester C=O), 1243 (ester CO), 720 cm^{-1} (axial CCl).

6α-Tosyloxy-3α-chloro-5α-cholestane (4b) was prepared in 83% yield from **4a** in the usual manner. The analytical sample was obtained after two crystallizations from 90% aqueous acetone: mp 139–139.5°; $[\alpha]^{23}D$ +28°; ir (CS_2) 1182 and 1162 (sym S=O), 720 cm^{-1} (axial CCl).

Anal. Calcd for $C_{34}H_{53}ClO_3S$: C, 70.73; H, 9.25; Cl, 6.14. Found: C, 70.92; H, 9.12; Cl, 6.33.

Product Analysis.—The products resulting from the solvolysis of both **2b** and **4b** at 90° in acetic acid solutions containing 0.04 *M* sulfonate, 0.08 *M* sodium acetate, and 0.08 *M* acetic anhydride were isolated by the usual ether extraction technique followed by chromatography over 70–325 mesh silicic acid.[7] Products were identified by comparison of their melting points and infrared spectra with those of authentic samples. The results obtained are listed in Table III.

Kinetic Measurements.—The usual sealed ampoule technique was used. The concentration of the sulfonate was 0.002 *M* in anhydrous acetic acid containing sodium acetate (0.004 *M*) and acetic anhydride (0.004 *M*). At appropriate time intervals 3-ml aliquots were quenched in ice water and stored at −15°. At the completion of the run the samples were warmed to 25° and transferred to a 1-cm silica cell whereupon the absorbance was determined using a Gilford Model 2000 spectrophotometer at 261 mμ at a slit width of 0.4 mm according to the method of Swain and Morgan.[14] Rate constants were calculated using a non-linear least-squares program.[15]

Registry No.—**2a**, 1251-93-0; **2b**, 31406-51-6; **3a**, 28398-68-7; **4a**, 1251-94-1; **4b**, 31354-63-9; **4c**, 31354-64-0.

(10) Experimental details have been given elsewhere.[6]

(11) O. Diels and P. Blumberg, *Ber.*, **44**, 2847 (1911).

(12) Professor Shoppee has kindly informed us that the originally reported rotation is in error, and that a new determination gives $[\alpha]D$ +63°, in chloroform. A mixture melting point with a sample generously supplied by Professor Shoppee showed no depression.

(13) E. S. Wallis, E. Fernholz, and F. T. Gephart, *J. Amer. Chem. Soc.*, **59**, 137 (1937).

(14) C. G. Swain and C. R. Morgan, *J. Org. Chem.*, **29**, 2097 (1964).

(15) LSKIN2, written by C. E. De Tar and D. F. De Tar, Florida State University, as modified by Dr. H. A. Hammond, University of California.

Synthesis of Adamantane Derivatives. XVII.[1] Facile Synthesis of Bicyclo[3.3.1]non-6-ene-3-aldehyde and -isopropyl alcohol

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Received April 13, 1971

Compared with the well-known ring-cleavage reactions of 1,3-disubstituted adamantanes,[2] those of 2,4-disubstituted adamantanes have been reported only recently.[3-5] In a previous publication[5] we reported that facile fragmentation reactions of 4(e)-methylsulfonoxyadamantan-2-one (**1**) with alkali, bromine, and lithium aluminum hydride afforded bicyclo[3.3.1]non-6-ene-3-carboxylic acid, 2(e)-bromo-4-oxahomoadamantan-5-one, and bicyclo[3.3.1]non-6-ene-3-carbinol (**4**), respectively. In this note, we wish to describe the successful application of this type of fragmentation reaction to the preparation of bicyclo[3.3.1]non-6-ene-3-aldehyde (**3**) and -isopropyl alcohol (**5**).

Treatment of **1** with sodium borohydride afforded a mixture of fragmentation products, from which **3** and **4** were isolated in 53 and 41% yields, respectively, both as oils after chromatography on a silica gel column. Aldehyde **3** exhibited ir absorptions (neat) at 2680, 1730, 1720 (sh), and 1645 cm^{-1} and had a M^+ at *m/e* 150. It gave the 2,4-dinitrophenylhydrazone (DNP) derivative, mp 210–211°. Alcohol **4** was identified as bicyclo[3.3.1]non-6-ene-3-carbinol by comparison of ir and nmr spectra and vpc retention time data with those of an authentic sample.[3,5] The

(1) Part XVI: T. Sasaki, S. Eguchi, and T. Toru, *Tetrahedron Lett.*, 1109 (1971).

(2) (a) H. Stetter and P. Tacke, *Angew. Chem.*, **74**, 354 (1962); (b) H. Stetter and P. Tacke, *Chem. Ber.*, **96**, 694 (1963); (c) C. A. Grob and W. W. Schwarz, *Helv. Chim. Acta*, **47**, 1870 (1965); (d) F. N. Stepanov and W. D. Suchowerchow, *Angew. Chem., Int. Ed. Engl.*, **6**, 864 (1967).

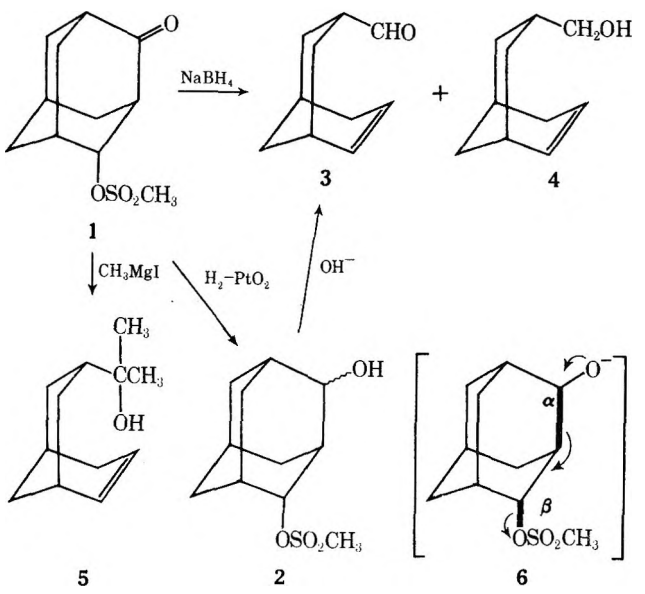
(3) For fragmentation of 4(e)-bromoadamantan-2-one with silver perchlorate to bicyclo[3.3.1]non-6-ene-3-carboxylic acid, see A. C. Udding, H. Wynberg, and J. Strating, *Tetrahedron Lett.*, 5719 (1968).

(4) For the Beckmann fission of adamantan-2-one oxime, see J. G. Korsloot and V. G. Keizer, *ibid.*, 3517 (1969).

(5) For the Schmidt fission of adamantan-2-one, see T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970).

formation of **3** and **1** can be explained by an alkaline-induced ring fragmentation of the initially formed alcohol **2** as shown in Scheme I. In fact, treatment of

SCHEME I



2 with ethanolic potassium hydroxide afforded aldehyde **3** in 60% yield. Alcohol **2** was easily obtained quantitatively as an oil by catalytic hydrogenation of **1** and had ir absorption bands (neat) at 3540, 3420, 1340 and 1185 cm^{-1} and nmr ($CDCl_3$) signals at δ 5.08–4.88 (m, 1, $CHOSO_2$), 4.15–3.95 (m, 1, CHOH), 3.22 (s, SO_2CH_3), 2.62 (s, 1, OH), and 2.50–1.40 (m, 12, other ring protons).

A further example of the facile ring cleavage of **1** was found in the reaction with Grignard reagent. Treatment of **1** with excess methylmagnesium iodide afforded alcohol **5**, mp 56–57°, in 75.5% yield, which was identified as bicyclo[3.3.1]non-6-ene-3-isopropyl alcohol by elemental analysis and direct comparison of spectral data and melting point with an authentic sample.[6]

The facile fragmentation aptitude of 2,4-disubstituted adamantanes can be understood in terms of the trans-coplanar geometry of the reacting bonds (α and β) in the intermediate as shown in **6**.[5,7] This is in good accordance with the results in the bicyclo[2.2.2]octane system reported recently by Kraus, *et al.*,[8] supporting the Grob hypothesis for fragmentation reactions.[9]

Experimental Section[10]

Reduction of 4(e)-Methylsulfonoxyadamantan-2-one (1) with Sodium Borohydride. Bicyclo[3.3.1]non-6-ene-3-aldehyde (3).—To a stirred solution of **1** (0.40 g, 1.6 mmol) in methanol (30 ml) was added a solution of sodium borohydride (0.90 g, 2.3 mmol) in aqueous methanol (80% v/v, 25 ml) under ice cooling. After stirring was continued for 2 days at room temperature, the mixture was concentrated under reduced pressure in order to remove methanol, diluted with water, acidified with acetic acid, and extracted with ether (five 20-ml portions). The combined ether extracts were dried (Na_2SO_4), and the solvent was removed to give an oily residue which was purified on a silica gel (Mallinckrodt, 100 mesh) column eluting with chloroform. The first fraction gave **3** (0.13 g, 53%) as a colorless oil.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.00; H, 9.71.

Treatment of **3** with 2,4-dinitrophenylhydrazine gave the 2,4-DNP of **3** as red crystals from ethanol–chloroform: mp 210–211°; nmr ($CDCl_3$) δ 11.09 (s, 1, C=NNH), 9.29–8.00 (m, 3, phenyl protons), 7.62 (d, J = 5.5 Hz, 1, CH=N), 6.05 (m, 2, CH=CH), and 2.70–1.40 (m, 11, remaining ring protons).

Anal. Calcd for $C_{16}H_{18}O_4N_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.13; H, 5.41; N, 16.84.

The second fraction gave alcohol **4** (0.10 g, 41%) as a colorless oil; the ir and nmr spectra and vpc retention time were identical with those of an authentic sample.[5]

Catalytic Reduction of 1. 2-Hydroxy-4-methylsulfonoxyadamantane (2).—A solution of **1** (1.0 g, 4.1 mmol) in methanol (20 ml) was hydrogenated in the presence of Adams catalyst (0.5 g) for 15 hr under atmospheric pressure at room temperature. After removal of the catalyst by filtration, the methanol solution was evaporated to dryness under reduced pressure to give **2** as an oil (0.99 g, 99%).

Anal. Calcd for $C_{11}H_{18}O_4S$: C, 53.63; H, 7.37. Found: C, 53.56; H, 7.43.

Alkaline Cleavage of 2 to 3.—Alcohol **2** (0.15 g, 0.61 mmol) was heated in 50% aqueous ethanol (8 ml) containing potassium hydroxide (0.20 g) at 60° for 6 hr. Work-up as usual afforded **3** in 60% yield.

Reaction of 1 with Methylmagnesium Iodide. Bicyclo[3.3.1]non-6-ene-3-isopropyl Alcohol (5).—A solution of **1** (0.50 g, 2.1 mmol) in dry tetrahydrofuran (5 ml) was added to a solution of methylmagnesium iodide in tetrahydrofuran (15 ml) prepared from methyl iodide (2.5 ml) and magnesium (turnings, 1.1 g, 45.3 mg-atoms). After refluxing for 6.5 hr, the cooled reaction mixture was diluted with water (50 ml), acidified with 10% hydrochloric acid, and extracted with ether (four 40-ml portions). Work-up as usual afforded an oily product which was purified on a silica gel column eluting with chloroform to give **5** (0.28 g, 75.5%) as colorless crystals from *n*-hexane: mp 56–57° (lit.[6] mp 56.5–58°); ir (KBr) 3450, 3250, 3160, 1635, and 1140 cm^{-1}; nmr ($CDCl_3$) δ 6.00–5.10 (m, 2, CH=CH), 1.50 (s, 1, OH), 1.14 (s, 6, $OC(CH_3)_2$), and 2.50–0.60 (m, *ca.* 11, other ring protons).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.77; H, 11.35.

Registry No.—**2**, 31662-18-7; **3**, 31603-46-0; **3** DNP, 31603-47-1; **5**, 28644-53-3.

(6) M. A. McKervey, D. Faulkner, and H. Hamill, *Tetrahedron Lett.*, 1971 (1970). Only the melting point is described herein.

(7) The fragmentation of homoadamantan-4-one systems does not seem to be as facile; *cf.* T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **36**, 2454 (1971).

(8) W. Kraus and W. Rothenwohrer, *Tetrahedron Lett.*, 1007 (1968); W. Kraus and C. Chassin, *Justus Liebigs Ann. Chem.*, **735**, 198 (1970); W. Kraus and C. Chassin, *Tetrahedron Lett.*, 1003, 1113 (1970).

(9) C. A. Grob, *Angew. Chem.*, **81**, 543 (1969); C. A. Grob and P. W. Schiess, *ibid.*, **79**, 1 (1967).

(10) *Cf.* footnote 27 in ref 5.

Tricarbethoxyphosphine

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Received December 31, 1970

As part of a program on the synthesis of new flame retardants for cotton, we were interested in preparing the tertiary phosphine containing three carboxamide substituents directly attached to phosphorus, $P(CONH_2)_3$. This compound, which is unknown, was to be prepared by ammonolysis of the corresponding triester, $P(CO_2Et)_3$ (I). Tertiary phosphines which contain one or two carbethoxy substituents are known,[2,3] but the triester I has not been described in the literature.

(1) One of the laboratories of the Southern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) A. Job and G. Dusollier, *C. R. Acad. Sci.*, **184**, 1454 (1927).

(3) K. Issleib and H. Anhöck, *Z. Naturforsch. B*, **16**, 837 (1961).

Tricarbethoxyphosphine (I) was prepared in 29% yield by the reaction of ethyl chloroformate with Na_3P.

$$Na_3P + 3ClCO_2R \longrightarrow P(CO_2R)_3 + 3NaCl$$
I, R = Et
II, R = Bu
III, R = Ph

The reaction stopped at the tertiary phosphine stage, despite the use of excess ethyl chloroformate. Alkyl chloroformates, unlike alkyl halides, do not quaternize tertiary phosphines, but tend to be decomposed by them with loss of CO_2.[4]

The yield, though low, represented the best of several trials. The most important variable was found to be the source of the trisodium phosphide, best results being obtained with the product of the reaction of white phosphorus with the green sodium–naphthalene radical anion in tetrahydrofuran.[5] Slightly lower yields (20–26%) were obtained with red phosphorus, which was safer but slower, but, when the Na_3P was prepared by the reaction of phosphorus trichloride[6] or white phosphorus[7] with sodium dispersed in toluene, no I was obtained at all, even though the ethyl chloroformate appeared to react.[8] The blue sodium–anthracene radical anion[9] gave a 23% yield of I, contaminated with 9,10-dihydroanthracene.[10]

Alternate routes, such as the reaction of ethyl chloroformate with the magnesium phosphide[11] $P(MgCl)_3$, or with phosphine in the presence of a tertiary amine such as triethylamine or dimethylaniline,[12] also failed to give any I.[13,14]

I was a colorless, mobile, air-stable liquid with a characteristic, sweet odor. It was soluble in organic solvents and insoluble in water. It gave no color reaction with carbon disulfide (in which it was insoluble), nor with benzoquinone nor benzofuroxan,[15,16] all characteristic tests for tertiary phosphines. It was recovered unchanged after 4 days with methyl iodide in tetrahydrofuran, and after treatment with aniline[17] or sulfur in boiling xylene.

In view of this demonstrated lack of reactivity, we were surprised to find that I instantly decolorized bromine in CCl_4 (or ethanol), and could be titrated quantitatively with this reagent. One mole of bromine was consumed per mole of I.[18]

Hydrolysis of I with 1 *N* NaOH took place rapidly at 100°, expelling phosphine.[19]

$$P(CO_2Et)_3 + 6NaOH \longrightarrow PH_3 + 3Na_2CO_3 + 3EtOH$$

After 3 hr at 100°, the reaction yielded 81.5% of phosphine and 86.5% of sodium carbonate. Under similar conditions, hydrolysis with 1 *N* HCl generated only 23% of phosphine.

Oxidation of I with 30% hydrogen peroxide took an unusual and unexpected course. Instead of the tertiary phosphine oxide, $O{=}P(CO_2Et)_3$, the reaction gave a 1:1 mixture of phosphorous acid and hypophosphorous acid. We could find no precedent for this in the literature. Hypophosphorous acid might be formed by a two-step sequence involving oxidation and hydrolysis.

$$P(CO_2Et)_3 + H_2O_2 \longrightarrow HOP(O)(CO_2Et)_2 + HCO_2Et$$
$$HOP(O)(CO_2Et)_2 + 2H_2O \longrightarrow H_3PO_2 + 2EtOH + 2CO_2$$

Further oxidation of the hypophosphorous acid by the 0.5 *M* excess of hydrogen peroxide used in the reaction would account for the presence of phosphorous acid in the reaction mixture. No formic acid was detected.[20]

Oxidation was even more vigorous when a base, sodium carbonate, was added to the reaction mixture. One mole of carbon dioxide was evolved for each mole of hydrogen peroxide employed.

The phosphine I also appeared to be destroyed by other oxidant systems, such as permanganate in acetone or bromine in ethanol.[21] The latter gave a 36% yield of an ester of phosphorous acid, *viz.* diethyl phosphonate, as one reaction product.

Mercuric chloride in ethanol was reduced by I to mercurous chloride (86%) after 5-hr refluxing, leaving an acidic residue. The Hg(II) salt, which often forms crystalline complexes with tertiary phosphines, functioned in this instance simply as a halogenating agent.

The reaction of I with ammonia in ethanol solution gave urea (91.5%) and an unstable oil, $n^{20}D$ 1.4764, which deposited an amorphous yellow solid on standing. The ir spectrum of the oil showed ester C–H and amide N–H bands but no P–H nor P–OH bands.[22] The oil and the yellow solid were not identified, but it is obvious that neither substance was the carboxamide, $P(CONH_2)_3$.

The results[23–27] of these experiments are assembled in

(4) H. J. Bestmann and K. H. Schnabel, *Justus Liebigs Ann. Chem.*, **698**, 106 (1966).

(5) D. J. Peterson, U. S. Patent 3,397,039 (Aug 13, 1968). We are indebted to Dr. T. J. Logan of the Procter & Gamble Co., Cincinnati, Ohio, for bringing this patent to our attention.

(6) L. Horner, P. Beck, and H. Hoffmann, *Chem. Ber.*, **92**, 2088 (1959).

(7) D. J. Peterson and T. J. Logan, *J. Inorg. Nucl. Chem.*, **28**, 53 (1966).

(8) The Na_3P prepared by the high-speed stirrer methods[6,7] appeared to be very finely divided, whereas the products of the radical anion routes were granular. All were black, including the PCl_3 product,[6] which contained 3 mol of NaCl.

(9) D. E. Paul, D. Lipkin, and S. I. Weissman, *J. Amer. Chem. Soc.*, **78**, 116 (1956).

(10) The carrier anthracene (or naphthalene) is usually regenerated when the Na_3P is formed, but in this experiment 5.1% of the 9,10-dihydro derivative, mp 107–108°, was isolated as a by-product.

(11) L. Horner and H. Hoffmann, "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Foerst, Ed., Academic Press, New York, N. Y., 1963, p 208.

(12) Ethyl chloroformate reacts vigorously with pyridine or triethylamine but not with dimethylaniline, not even when heated.

(13) The salt $[Et_3NCO_2Et]Cl$, obtained as a thick slurry in ether at ice-bath temperature,[14] was slowly decomposed by phosphine at room temperature giving 15% of triethylamine hydrochloride, mp 254–255°, as the only nonvolatile product.

(14) M. Matzner, R. P. Kurkjy, and R. C. Cotter, *Chem. Rev.*, **64**, 645 (1964).

(15) A. S. Bailey, J. M. Peach, C. K. Prout, and T. S. Cameron, *J. Chem. Soc. C*, 2277 (1969).

(16) J. H. Boyer and S. E. Ellzey, Jr., *J. Org. Chem.*, **26**, 4684 (1961).

(17) In an attempt to prepare the known compound $P(CONHPh)_3$, mp 212–213°: S. A. Buckler, *ibid.*, **24**, 1460 (1959).

(18) Triphenylphosphine, in contrast, cannot be titrated with bromine in CCl_4, as it consumes much more than the amount required for the formation of the 1:1 adduct Ph_3PBr_2.

(19) The components R_2PCO_2Et (R = Et, Ph, C_6H_{11}) similarly yield R_2PH upon hydrolysis with alkali.[3]

(20) The occurrence of ethyl formate as one of the reaction products seems to be required by the stoichiometry. There was not enough hydrogen peroxide present for the reaction $P(CO_2Et)_3 + 2H_2O_2 + H_2O \rightarrow H_3PO_2 + 3EtOH + 3CO_2$.

(21) A. W. Frank and C. F. Baranauckas, *J. Org. Chem.*, **31**, 872 (1966).

(22) Ir (neat, taken at once) 1070 s, 1098 m, 1175 m br, 1335 s, 1377 s, 1412 m, 1450 w, 1470 w, 1610 m, 1670 m, 1720 vs (C=O), 3000 w (CH), 3225 w (NH), 3380 s (NH), 3500 s cm^{-1} (NH).

(23) W. E. White and A. H. Bushey, *J. Amer. Chem. Soc.*, **66**, 1966 (1944).

(24) D. A. Skoog and D. M. West, "Fundamentals of Analytical Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1966, p 352.

(25) A. I. Vogel, "A Textbook of Macro and Semimicro Qualitative Inorganic Analysis," 4th ed, Longmans, Green and Co., London, 1954, p 392.

(26) P. Lemoult, C. R. *Acad. Sci.*, **142**, 1193 (1906).

(27) A. E. Arbuzov and B. A. Arbuzov, *J. Prakt. Chem.*, [2] **130**, 103 (1931).

Table I. In retrospect, it appeared that I was reactive only toward reagents which affected the ester groups (with the exception of bromine), suggesting a very low order of nucelophilicity for the phosphorus atom. To obtain a measure of the basicity of I, a measurement

TABLE I

SUMMARY OF REACTIONS WITH I

Reagent	Solvent	Conditions	Products (% yield)
NaOH	H_2O	100°, 3 hr	PH_3 (81.5),[a] Na_2CO_3 (86.5)[b]
HCl	H_2O	100°, 3 hr	PH_3 (23),[a] I (28)
H_2O_2	Acetone	RT, 15 min	H_3PO_2 (42.4), H_3PO_3 (45.5)[c]
$H_2O_2(Na_2CO_3)$	Acetone	RT,[d] 15 min	$NaHCO_3$ (89)[b]
Br_2	EtOH	0–10°, 5 min	$(EtO)_2P(O)H$ (36)[e]
$HgCl_2$	EtOH	78°, 5 hr	Hg_2Cl_2 (86)
NH_3	EtOH	RT,[f] 30 min	Urea (91.5)[g]

[a] Analyzed by the $HgCl_2$ method;[23] bromphenol blue was found to be a useful indicator for this titration. [b] Analyzed by the Winkler method.[24] [c] By titration with 0.1 *N* NaOH. H_3PO_2 confirmed by tests with copper sulfate and potassium permanganate,[25] and H_3PO_3 by precipitation as the aniline salt, mp 167–169° (lit.[26] mp 179°); H_3PO_4 absent. [d] Exotherm to 56°. [e] Bp 47° (0.2 mm), $n^{20}D$ 1.4560 [lit.[27] bp 51–52° (2 mm), $n^{20}D$ 1.4082]. Refractive index high because sample contained naphthalene (ir). [f] Exotherm to 40°. [g] Mp 132–133°, confirmed as urea by ir and biuret test.

was made of the shift of the OD peak of methanol-*d* induced by I in the infrared spectrum of a solution of CH_3OD in CCl_4. From this measurement, the pK_a of I was calculated[28] to be −10.9, an exceedingly low figure. The tributyl ester II gave a similar figure, pK_a = −10.4.

Calculation of the base strength of the tertiary phosphine $P(CO_2Me)_3$, using the appropriate Henderson–Streuli equation[29] and Taft substituent constant,[30] gives a pK_a of −8.17 for this ester. The actual values for I and II were somewhat lower than this, but within the limits of accuracy of method ($pK_a = \pm 2$). Normal pK_a values for tertiary phosphines, R_3P, are in the 8–9 range, *e.g.*, 8.69 for R = Et, but extend as low as 2.73 for R = Ph and 1.36 for R = CH_2CH_2CN.[29]

Two other phosphine triesters were prepared by the reaction of trisodium phosphide with the appropriate chloroformate ester. The tributyl ester $P(CO_2Bu)_3$ (II), bp 147° (0.2 mm), was prepared in 27% yield by the reaction of trisodium phosphide with butyl chloroformate, and the triphenyl ester, $P(CO_2Ph)_3$ (III), mp 125–126°, in 7% yield, together with 22% of diphenyl carbonate, by the reaction of trisodium phosphide with phenyl chloroformate. Methyl chloroformate decomposed on contact with the phosphide.

Experimental Section[31]

Starting Materials.—Commercial reagents were generally used without further purification. The tetrahydrofuran (Eastman White Label)[32] used in the first preparation of I was dried over KOH and distilled from lithium aluminum hydride. Later, it was discovered that the green sodium–naphthalene radical anion was formed in less than 5 min even when the solvent was not purified. The stabilizer (0.025% BHT) in the solvent evidently did not interfere. The solvent was used thereafter as obtained.

Tricarbethoxyphosphine (I).—Ethyl chloroformate (21.7 g, 0.2 mol) was added dropwise to a well-stirred slurry of trisodium phosphide[5] (4.0 g, 0.04 mol) in tetrahydrofuran (100 ml), with ice-cooling applied as necessary to moderate the mild exotherm. The mixture was then heated briefly to reflux, allowed to cool to room temperature, and treated cautiously with anhydrous ethanol (25 ml) to decompose any excess Na or Na_3P. The mixture was filtered under vacuum through a fine, fritted-glass filter (very slow), giving 7.5 g of yellow, malodorous, water-insoluble solid,[33] and a filtrate which, when concentrated, left 9.4 g of yellow liquid. A Beilstein test for Cl on the liquid was negative, but the liquid still contained the naphthalene (1.5 g) which had been used in the preparation of the Na_3P.[5] The naphthalene was removed by distillation at 130° bath temperature (1.0 mm), the apparatus being disassembled and cleaned several times until no more naphthalene distilled.[34] The product was then distilled, giving 2.9 g (29%) of I, bp 130° (1.0 mm), $n^{20}D$ 1.4678, as a colorless, mobile liquid with a sweet odor: ir (neat) 777 w, 848 m, 1010 s, 1095 sh, 1135 vs, 1175 vs, 1210 s, 1290 w, 1360 w, 1385 w, 1445 w, 1465 w, 1730 vs (C=O), 3000 m cm^{-1} (CH); nmr (neat) δ 1.28 (t, 9 H, CH_3, J = 7.0 Hz), 4.28 ppm (q, 6 H, CH_2, J = 7.0 Hz); ^{31}P δ −3.37 ppm.

Anal. Calcd for $C_9H_{15}O_6P$: C, 43.20; H, 6.04. Found: C, 43.44; H, 6.14.

The compound was soluble in ethanol, benzene, CCl_4, and THF, but insoluble in water.

The preparation was repeated on a 15-fold scale, giving 64.4 g (26%) of I, bp 129–131° (1.4 mm). On this scale, filtration of the reaction mixture would have been tedious. Fortunately, it was discovered that the reaction mixture could be partitioned between benzene and water, despite the presence of large volumes of ethanol (250 ml) and THF (2500 ml). The reaction mixture was diluted with an equal volume of water and extracted three times with benzene, giving 244.1 g of a dark red oil from which I was obtained by distillation.

Titration of I with Bromine.—A 0.259-g sample of I in 5 ml of CCl_4 was titrated rapidly with 0.135 *M* Br_2 in CCl_4 to a permanent yellow end point. The phosphine consumed 7.80 ml of the bromine reagent, corresponding to 1.02 mol of Br_2 per mole of I.

I also decolorized I_2 in CCl_4, but not I_2 in benzene.

Tris(butoxycarbonyl)phosphine (II).—The reaction of 47.8 g (0.35 mol) of butyl chloroformate with 10.0 g (0.1 mol) of trisodium phosphide in 250 ml of tetrahydrofuran gave 17.1 g of distilled product which, when redistilled, gave fractions (a) 0.8 g, bp 110–147° (0.2 mm), $n^{20}D$ 1.4602; (b) 4.7 g, bp 147° (0.2 mm), $n^{20}D$ 1.4646; and (c) 8.2 g, bp 147–149° (0.2 mm), $n^{20}D$ 1.4668. The yield of II was 12.9 g (27%). Fraction b data: ir (neat) 738 w, 790 w, 830 w, 900 w, 926 m, 960 w, 990 w, 1012 w, 1055 w, 1135 vs, 1200 s, 1235 m, 1375 w, 1465 m, 1725 vs (C=O) and 2970 cm^{-1} (CH); ^1H nmr ($CDCl_3$),[35] δ 0.93 (t, 9 H, CH_3, J = 7.0 Hz), 1.1–1.9 (m, 12 H, $CH_2CH_2CH_3$), and 4.33 ppm (t, 6 H, OCH_2, J = 6.5 Hz); ^{31}P nmr (neat) δ −3.85 ppm.

Anal. Calcd for $C_{15}H_{27}O_6P$: C, 53.88; H, 8.14; P, 9.27. Found: C, 54.01; H, 8.27; P, 9.29.

Tris(phenoxycarbonyl)phosphine (III).—The reaction of 54.8 g (0.3 mol) of phenyl chloroformate with 10.0 g (0.1 mol) of trisodium phosphide in 300 ml of tetrahydrofuran gave, after stripping off the naphthalene and some volatile liquid at 130° (0.5 mm), an oil which solidified on cooling to a hard mass of crystals (33.4 g). The crude product was taken up in a large volume (500 ml) of warm ethanol and filtered, giving 9.0 g of dark yellow, amorphous solid (discarded). The filtrate was concentrated and recrystallized once from ethanol, giving 2.75 g (7%) of III:

(28) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

(29) W. A. Henderson, Jr., and C. A. Streuli, *J. Amer. Chem. Soc.*, **82**, 5791 (1960).

(30) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 619.

(31) Melting points are corrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra, with the exception of those used for the basicity measurements, were taken on a Perkin-Elmer Model 137B instrument with NaCl optics. ^1H nmr spectra were taken on a Varian A-60 spectrometer using TMS as internal standard, and ^{31}P nmr on a Varian HA-60-IL instrument at 24.3 Mcps, using 85% H_3PO_4 as external standard.

(32) Naming of firms or their products in this paper does not imply their endorsement by the Department of Agriculture.

(33) In subsequent runs the solid was mixed with Filter-aid to aid in its removal. Its color varied from yellow to olive-brown.

(34) Naphthalene was easily detected in the product by its ir absorption at 788 cm^{-1}.

(35) This spectrum bore a striking resemblance to that of dibutyl carbonate, in "High Resolution NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, No. 243.

pale yellow needles; mp 125–126°; ir (Nujol) 686 s, 740 vs, 794 m, 833 w, 848 m, 918 m, 1002 m, 1022 m, 1105 vs, 1160 s, 1176 s, 1486 m, 1587 w (C=C aromatic) and 1733 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.35 ppm (m).

Anal. Calcd for $C_{21}H_{15}O_6P$: C, 63.96; H, 3.85; P, 7.86. Found: C, 63.48; H, 4.14; P, 7.67.

III is soluble in benzene and in warm methanol and insoluble in water or carbon tetrachloride.

The mother liquor from the recrystallization of III was concentrated to low volume, filtered, and evaporated to dryness, giving 7.05 g (22%) of pale yellow, crystalline solid, mp 70–72°, identified by its ir spectrum as impure diphenyl carbonate. The melting point was raised to 76.5–77.5° (lit.[36] mp 79°) by recrystallization from methanol–water.

Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 71.43; H, 4.56; P, 0.86.

The phenyl chloroformate used in this reaction did not contain any diphenyl carbonate (ir). The diphenyl carbonate is therefore a by-product of the reaction with Na_3P.

Basicity Measurements.—The base strengths of I and II were determined by the MeOD method,[28] using 0.5 mm cells and a grating instrument (Perkin-Elmer 421) calibrated with polystyrene. The spectra were scanned from 2800 to 2200 cm^{-1}. A 0.25 *M* solution of MeOD in CCl_4 showed a strong, sharp peak at 2680 cm^{-1} (ν_{OD} free) and a strong, broad peak at 2482 cm^{-1} (ν_{OD} bonded, owing to self-association of the MeOD). Upon the addition of a base (1.0 *M*), the 2680-cm^{-1} peak diminished in intensity and the 2482-cm^{-1} peak shifted and became stronger. Observed shifts for various bases, relative to the 2680-cm^{-1} peak, were $\Delta\nu$ 120 (DMF), 100 (dioxane, lit.[28] 111), 65 (CH_3CN, lit.[28] 63), 35 (I), and 40 cm^{-1} (II).

Using the data, and the expression $pK_a = 0.1[\Delta\nu] - 14.4$ derived from Arnett's Figure 5,[28] the base strengths of I and II were calculated to be $pK_a = -10.9$ and -10.4, respectively.

The phenyl ester III was not sufficiently soluble in CCl_4 to obtain a measurement.

Registry No.—I, 31081-90-0; II, 31128-88-8; III, 31128-89-9.

Acknowledtments.—We are indebted to Dr. R. H. Dinius, Auburn University, for the ^{11}P nmr spectra, and to Mr. G. J. Boudreaux and Miss E. R. McCall of this Laboratory for the ^1H nmr spectra and ir basicity measurements, respectively.

(36) P. D. Ritchie, *J. Chem. Soc.*, 1054 (1935).

Photolysis and Pyrolysis of 2-Azido-3-nitronaphthalene

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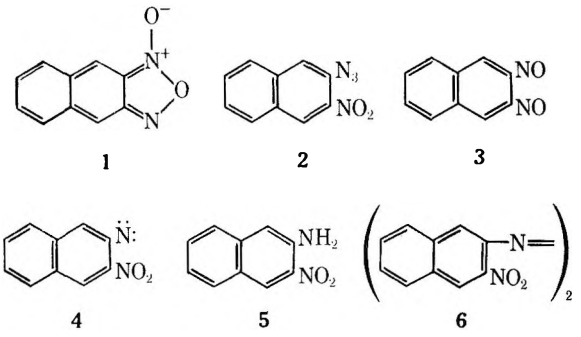
To test the formation of an apparently unfavorable quinonoid system contained in naphtho[2,3-*c*]furoxan (**1**), the expulsion of nitrogen from 2-azido-3-nitronaphthalene (**2**) has been investigated.[1,2] As expected, both irradiation and heat bring about the release of molecular nitrogen; however, neither the furoxan nor its isomer, 2,3-dinitrosonaphthalene (**3**), could be detected.

Consideration of the greater thermal stability of 5-nitro- and 8-nitro-2-azidonaphthalene[3] over 1-nitro-2-azidonaphthalene and the isomer **2** provides an explanation for an increased facility in the release of nitrogen from **2** through anchimeric assistance by the adjacent nitro group. In the present instance, no products in which a new NO bond is formed were isolated. The reaction apparently leads to the intermediate 3-nitronapthyl-2-nitrene (**4**). Hydrogen abstraction from the solvent with the formation of 2-amino-3-nitronaphthalene (**5**) in both thermal and photoelimination reactions is diagnostic of the nitrene intermediate. The additional photogeneration of 3,3′-dinitro-2,2′-azonaphthalene (**6**) is best accounted for by interaction between the azide **2** and the nitrene **4**.



Experimental Section[4]

After nitrogen was flushed through a solution of the azide **2** (200 mg, 0.93 mmol) in anhydrous benzene for 16 hr, it was irradiated with 254-nm low-pressure mercury lamps in a Rayonet chamber reactor and the reaction was monitored by ir. After 1.5 hr of irradiation the solution was concentrated under vacuum (60°). The residue was triturated with benzene (10 ml), filtered, and twice recrystallized from nitromethane as red needles of 2,2′-dinitroazonaphthalene (33 mg, 18.5%): mp 365–370° dec; ν max (KBr) 1520 and 1340 cm^{-1} (NO_2); mass spectrum *m/e* 372 (M^+, parent peak), 356 $(M - O)^+$, 340 $(M - O_2)^+$, 310 $(M - NO_2 - O)^+$, 200 $(M - C_{10}H_6NO_2)^+$, 144 $(C_9H_6NO)^+$, 114 $(C_9H_6)^+$, and 57 $(C_9H_6)^{2+}$; λ_{max} ($CHCl_3$) 290 nm (ε 38,370) and 390 (17,740).

Anal. Calcd for $C_{20}H_{12}N_4O_4$: C, 64.52; H, 3.22; N, 15.06; mol wt, 372. Found: C, 64.46; H, 3.18; N, 15.27.

The benzene filtrate was concentrated and the residual solid was purified by chromatography over a column of silica gel (10 × 1 in.). Elutions with a 1:1 hexane–benzene mixture (450 ml) gave 2-azido-3-nitronaphthalene (6 mg, 3%), mp and mmp (with an authentic sample) 101–102°. Subsequent elutions with the same solvent mixture (600 ml) and a 1:2 mixture (300 ml) gave a red residue. It was treated with Norit in benzene and recrystallized from hexane as microscopic red needles of 2-amino-3-nitronaphthalene (8.5 mg, 4.5%): mp and mmp (with the authentic sample) 108–109°; ir (KBr) superposable with the authentic spectrum. Further elutions with polar solvents afforded an intractable resinous product.

A solution of the azide (200 mg, 0.94 mmol) in anhydrous octane (10 ml) was heated at 100° with stirring for 8 hr while the reaction was monitored by tlc. From the dark reaction mixture the solvent was removed under vacuum [50° (25 mm)]. The residue upon tlc examination, using ChromAR-500 sheets with benzene and ethyl acetate solvents, indicated the presence of the unreacted 2-azido-3-nitronaphthalene and 2-amino-3-nitronaphthalene. The residue was purified by chromatography

(1) A. Rahman, A. J. Boulton, D. P. Clifford, and G. J. T. Tiddy, *J. Chem. Soc. B*, 1516 (1968), reported stability of the azide **2** which is inconsistent with the present observations.

(2) The azide was prepared from 2,3-dinitronaphthalene.[1] A sample of this dinitro derivative was obtained from the Fundamental Research Company, Berkeley, Calif.

(3) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **91**, 1942 (1907), reported 5-nitro-2-azidonaphthalene, mp 133.5° (no decomposition) and stability in boiling glacial acetic acid; 8-nitro-2-azidonaphthalene, mp 108° (no decomposition); 1-nitro-2-azidonaphthalene, mp 116–117° (vigorous decomposition) and slow evolution of nitrogen when heated in ethanol.

(4) Microanalyses by Micro-Tech Laboratories, Skokie, Ill. Instrumental data were obtained from a Perkin-Elmer 237-B infrared spectrophotometer, a Cary-14 ultraviolet spectrometer, a Perkin-Elmer 270 mass spectrometer, a Varian Aerograph 1800 gas chromatograph, and a Reichert microscope melting point apparatus.

over silica gel (12 × 1 in.). A 1:1 mixture of hexane–benzene (33 ml) eluted 2.2 mg of a pink residue which was found to contain, by gc (5% SE-30)–mass spectral analysis, four volatile fractions with molecular ions m/e 139, 226 ($C_{16}H_{34}$),[5] 173 ($C_{10}H_7NO_2$),[6] and 253 (probably $C_{18}H_{23}N$) in their order of appearance. A mixture of hexane–benzene (1:2, 400 ml) eluted 2-azido-3-nitronaphthalene (55 mg, 28%): mp and mmp (with the authentic sample) 101–102°; ir (CH_2Cl_2) superposable with that of the authentic material. A 1:3 mixture of the same solvents (600 ml) eluted 2-amino-3-nitronaphthalene (3.8 mg, 3.9%). Gc analysis over a 3% SE-30 column (6 ft × 1/8 in., at 200°, Varian-1800 gas chromatograph) confirmed the presence of 2-amino-3-nitronaphthalene associated with trace amounts of an unidentified impurity. Further elutions with chloroform and a chloroform–ethanol mixture (9:1) gave a dark intractable solid which charred upon vacuum sublimation.

Registry No.—**2**, 22496-30-6; **5**, 13115-28-1; **6**, 31417-80-8.

(5) Assumed to be a combination of solvent radicals.
(6) Assumed to be β-nitronaphthalene.

The Reaction of Dithiazolium Cations with Sodium Azide

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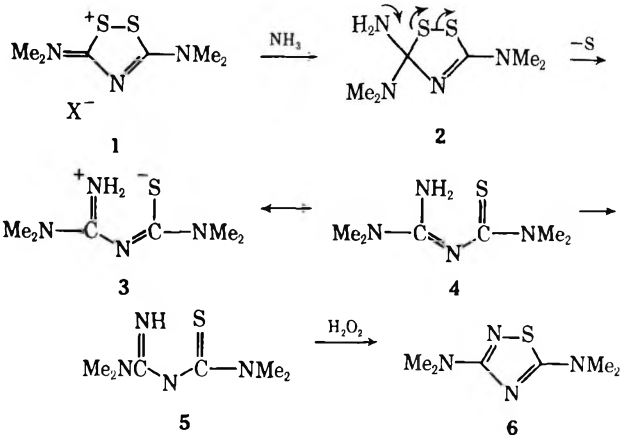
3,5-Bis(dimethylamino)-1,2,4-dithiazolium chloride (**1**, X = Cl) and a number of closely related dithiazolium salts are chemosterilants against house flies (*Musca domestica* L.).[1] To see whether similar biological activity might be found in geometrically similar, uncharged heterocyclic compounds, we wished to prepare a series of bis(dimethylamino) heterocyclic compounds including the 1,2,4-thiadiazole **6**. Various syntheses of amino-1,2,4-thiadiazoles have been developed,[2] but many of them give only mono- or unsubstituted amino groups. 3,5-Diamino-1,2,4-thiadiazoles can be prepared by oxidation of amidinothioureas,[2,3] and, since amidinothioureas can be made by reacting iminodithiazolidine salts and amines,[3] we were able to prepare **6** from **1** as shown in Scheme I. The overall yield of **6** was about 25%.[1b] The probable mechanism[3,4] of the addition of ammonia presumably involves ring opening and extrusion of elemental sulfur, assisted by an electron pair from either the amino or dimethylamino group of **2**.

The immediate species after loss of sulfur is interesting. Resonance form **3** suggests that the remaining sulfur should be rather nucleophilic, and we reasoned that, if the ring opening were initiated by a nucleophile that contained an inherent electrophilic center, direct cyclization might occur. To test this hypothesis we reacted **1** with sodium azide (NaN_3).

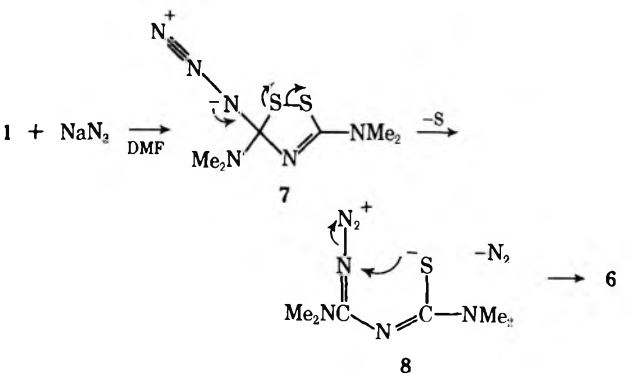
When **1** and NaN_3 were heated together in water, no reaction occurred. However, in dimethylformamide

SCHEME I



(DMF), an intense blue color quickly developed, and at about 80° nitrogen was evolved. In a few minutes the color was discharged, and the product, obtained in 75% yield after distillation, was the same 1,2,4-thiadiazole prepared earlier. The rationale is shown in Scheme II.

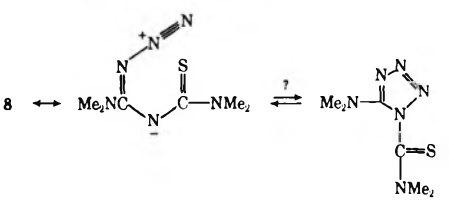
SCHEME II



The N_2^+ end of the azide function evidently creates the desired electrophilic center and also serves as a good leaving group.[5]

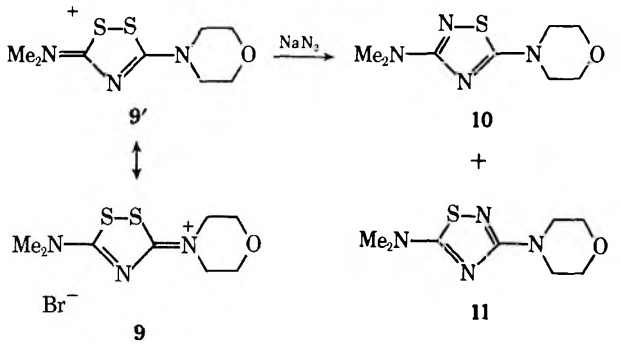
3,5-Dipiperidino-1,2,4-dithiazolium bromide reacted analogously with NaN_3 to give a good yield of 3,5-dipiperidino-1,2,4-thiadiazole. We then tried the reaction on an unsymmetrically substituted dithiazolium salt and chose the dimethylaminomorpholino compound **9,9′** with the hope that the rather large difference in basicity[6] between dimethylamine (pK_B = 3.36) and morpholine (5.64) might result in selective nucleophilic attack at one of the two ring carbons. Although **9,9′** was somewhat less reactive than **1**, it did react smoothly

(1) (a) R. L. Fye, G. C. LaBrecque, A. B. Bořkovec, and J. Morgan, Jr., *J. Econ. Entomol.* **62**, 522 (1969); (b) J. Oliver, S. C. Chang, R. T. Brown, J. B. Stokes, and A. B. Bořkovec, unpublished results.
(2) F. Kurzer, *Advan. Heterocycl. Chem.*, **5**, 119 (1965).
(3) (a) S. N. Dixit, *J. Indian Chem. Soc.*, **37**, 151 (1960); (b) *ibid.*, **38**, 221 (1961).
(4) Nucleophilic additions to the closely related 1,2-dithiolium cations have been studied in some detail. For a review see H. Prinzbach and E. Futterer, *Advan. Heterocycl. Chem.*, **7**, 39 (1966).
(5) The editor has pointed out that intermediate **8** is very similar to the proposed intermediates in the thermal isomerizations of 5-aminotetrazoles: R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Amer. Chem. Soc.*, **76**, 88 (1954); **77**, 2264 (1955). Thus **8** could possibly have closed to a thiocarbamoyltetrazole. We have no evidence that such a reaction occurred; however, the isolated thiadiazoles were usually much more soluble than most tetrazoles, and small amounts of the latter could have escaped detection.



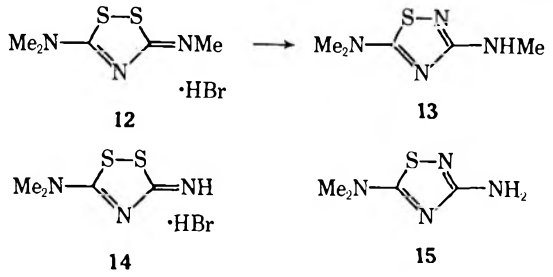
(6) H. K. Hall, *ibid.*, **79**, 5441 (1957).

with NaN_3 in dimethyl sulfoxide (DMSO) to give a 76% yield of crude thiadiazoles (**10** + **11**). The anticipated selectivity was not observed, however, as a 1:2 mixture of the two isomers was obtained. Pure samples of both **10** and **11** were obtained by preparative gas



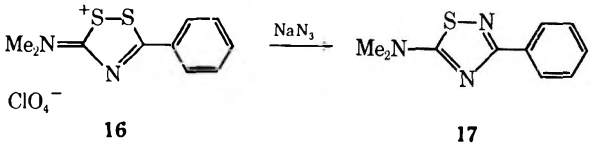
chromatography, but the physical data have not allowed us to unambiguously distinguish which isomer is which. More important, we feel, is the lack of selectivity in spite of the difference in basicities of the substituents.

Dimethylaminomethylimino- and dimethylaminoimino-1,2,4-dithiazolidines (as their hydrobromides **12** and **14**) similarly reacted with NaN_3 in DMF to give the 5-(dimethylamino)-3-(methylamino)- and 3-amino-5-(dimethylamino)-1,2,4-thiadiazoles (**13** and **15**, respectively). The yields of pure **13** and **15** were 40–60%; the other isomers were not detected. These products



correspond to attack by N_3^- at the carbon bearing the less highly substituted amine.

Finally we reacted NaN_3 with 5-(dimethylamino)-3-phenyl-1,2,4-dithiazolium perchlorate (**16**). The product was the known[7] 5-(dimethylamino)-3-phenyl-1,2,4-thiadiazole (**17**). Though the yield of recrystallized **17** was only about 25%, we were unable to detect any of the other isomer in the crude reaction mixture. It is interesting that nucleophilic attack has occurred on the phenyl-substituted carbon instead of on the carbon adjacent to the exocyclic nitrogen (which must bear most of the positive charge).[8]



An interesting aspect of these reactions is the color that usually accompanied them. The color normally began to develop almost immediately upon heating a mixture of a dithiazolium salt and NaN_3 in DMF or DMSO, well before the reactants had completely dissolved. Often a pale green color developed first that rather quickly changed to an intense blue. Although the color was occasionally discharged in a few minutes, this was frequently not the case and intensely colored solutions sometimes remained after the reactions had gone to completion, although a deep red-brown usually replaced the original blue. This phenomenon is not specific to dithiazolium salts, however; we have found that a variety of sulfur-containing compounds—dithiobiurets, monothiobiurets, tetralkylthioureas, 1,2,4-dithiazolidine-3-thiones—and sulfur itself also produce blue or blue-green colors when heated with NaN_3 in DMF. Although we do not know the cause of the colors, we feel that they are not necessarily associated with any of the intermediates between the dithiazolium salts and thiadiazoles. For example, the reaction of **14** and NaN_3 did not produce a blue solution although the expected product was obtained.

(7) J. Goerdeler and K. H. Heller, *Chem. Ber.*, **97**, 225 (1964).

(8) Nucleophiles have been reported to similarly attack C-5 of 5-phenyl-1,2,4-dithiazole-3-thione: J. Vialle, *Quart. Rep. Sulfur Chem.*, **5**, 151 (1970).

Experimental Section[9]

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Model T-60 spectrophotometer and infrared spectra were obtained on a Perkin-Elmer Model 137 sodium chloride prism spectrophotometer. Gas chromatographic separations were achieved on an Aerograph Autoprep Model A-700 gas chromatograph. Mass spectra were recorded on a Finnigan Model 1015 quadrapole mass spectrometer. Magnesium sulfate was used as a drying agent. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Caution: Although we experienced no difficulties with any of these reactions, normal precautions should be observed when heating azides and perchlorates.

Preparation of Dithiazolium Bromides.—The general procedure was that described for the preparation of 3,5-bis(dimethylamino)-1,2,4-dithiazolium bromide (**1**, X = Br).[10] A mixture of dimethylthiocarbamoyl chloride (0.1 mol) and KSCN (0.1 mol) in acetone (90 ml) was stirred and refluxed 15 min and then cooled. The KCl was removed by filtration and the bright yellow filtrate was cooled in an ice bath. The appropriate amine (Me_2NH, morpholine, $MeNH_2$, or NH_3, 0.1 mol) in water or acetone was added dropwise; after *ca.* 30 min HBr (48%, 0.1 mol) and H_2O_2 (30%, 0.1 mol) were added dropwise in that order. The dithiazolium bromides were collected by filtration, washed with acetone, and recrystallized (usually EtOH–H_2O). Yields were 50–70%.

(Dimethylamino)morpholino-1,2,4-dithiazolium bromide (**9**,**9′**) had mp 208–210° dec.

Anal. Calcd for $C_8H_{14}N_3OS_2Br$: C, 30.77; H, 4.52; N, 13.45; S, 20.54. Found: C, 30.54; H, 4.83; N, 13.40; S, 20.57.

(Dimethylamino)(methylimino)-1,2,4-dithiazolidine hydrobromide (**12**) had mp 248–249°.

Anal. Calcd for $C_5H_{10}N_3S_2Br$: C, 23.44; H, 3.93; N, 16.40. Found: C, 23.28; H, 3.89; N, 16.44.

(Dimethylamino)imino-1,2,4-dithiazolidine hydrobromide (**14**) had mp 215–219°.

Anal. Calcd for $C_4H_8N_3S_2Br$: C, 19.84; H, 3.33; N, 17.35. Found: C, 19.60; H, 3.28; N, 17.49.

3,5-Dipiperidino-1,2,4-dithiazolium bromide was prepared in the same way from pentamethylene thiocarbamoyl chloride.[11] It had mp 258–260° dec.

Anal. Calcd for $C_{12}H_{20}N_3S_2Br$: C, 41.14; H, 5.75; N, 11.99. Found: C, 40.97; H, 5.87; N, 11.89.

5-(Dimethylamino)-3-phenyl-1,2,4-dithiazolium Perchlorate (16).—Aqueous Me_2NH (1.7 ml, 40%) was added to glacial HOAc (90 ml), and then 5-(methylthio)-3-phenyl-1,2,4-dithi-

(9) Mention of a proprietary product or company does not necessarily imply endorsement by the U. S. Department of Agriculture.

(10) W. R. Diveley, U. S. Patent 3,166,564 (Jan 19, 1965); *Chem. Abstr.*, **62**, 9145g (1965).

(11) W. Ried, H. Hillenbrand, and G. Oertel, *Justus Liebigs Ann. Chem.*, **590**, 123 (1954).

azolium perchlorate[12] (4.35 g) was added. The mixture was stirred and heated to reflux at which time a homogeneous solution resulted. The solution was filtered and cooled; **16** was collected and recrystallized again from HOAc to give 1.01 g, mp 189–190.5° (23%; another modification has mp 176°).

Anal. Calcd for $C_{10}H_{11}ClN_2O_4S_2$: C, 37.21; H, 3.44; N, 8.68; S, 19.87. Found: C, 37.21; H, 3.33; N, 8.85; S, 20.00.

After collection of **16**, the HOAc filtrate was evaporated to dryness, and the residue was extracted with $CHCl_3$. The material thus obtained was recrystallized from hexane–EtOAc to give 0.55 g (20%) of methyl benzoyldithiocarbamate, mp 133–135°, that was identical with the authentic material.[13]

Reaction of 1 (X = Br) with NaN_3.—A mixture of **1** (8.46 g, 0.0314 mol) and NaN_3 (2.2 g, 0.034 mol) in DMF (75 ml) was stirred under nitrogen while the flask was heated in an oil bath. A deep blue color quickly developed. At 80–85° vigorous gas evolution was observed. The solution was kept at 85–90° for 1 hr, and the most of the DMF was removed *in vacuo*. Benzene was added, and the solution was filtered and distilled to give 4.1 g (76%) of 3,5-bis(dimethylamino)-1,2,4-thiadiazole [**6**, bp 120–126° (0.5–0.6 mm)], identical with that synthesized previously).[1b]

Reaction of 3,5-Dipiperidino-1,2,4-dithiazolium Bromide with NaN_3.—The reaction was run as described for the reaction of **1**; a 94% crude yield of 3,5-dipiperidino-1,2,4-thiadiazole was obtained as a light yellow oil. Partial decomposition occurred on attempted distillation [>150° (0.15 mm)] and the distillation was interrupted. Upon cooling, the material remaining in the flask solidified. Two recrystallizations from MeOH–H_2O gave the pure compound, mp 65–66°.

Anal. Calcd for $C_{12}H_{20}N_4S$: C, 57.10; H, 7.99; N, 22.20; S, 12.71. Found: C, 57.24; H, 8.03; N, 22.14; S, 12.51.

Reaction of 9 with NaN_3.—This reaction was run similarly except DMSO was used as the solvent (heated to 100°). The product was obtained by adding H_2O and extracting thoroughly with ether; a 76% yield of crude 3-(dimethylamino)-5-morpholino-1,2,4-thiadiazole (**10**) and 5-(dimethylamino)-3-morpholino-1,2,4-thiadiazole (**11**) was obtained from which samples of the pure compounds were obtained by preparative gas chromatography (5 ft × 0.25 in. 10% Carbowax 20M on 60–80 Chromosorb W, 190°). The collected samples were each recrystallized from hexane:

Isomer A (*ca.* 33%), mp 89–90°, had retention time 25 min; δ ($CDCl_3$) 3.04 (Me_2N).

Anal. Calcd for $C_8H_{14}N_4OS$: C, 44.84; H, 6.58; N, 26.15; S, 14.92. Found: C, 44.63; H, 6.61; N, 26.02; S, 15.02.

Isomer B (*ca.* 67%), mp 79°, had retention time 32.5 min; δ ($CDCl_3$) 3.08.

Anal. Calcd for $C_8H_{14}N_4OS$: C, 44.84; H, 6.58; N, 26.15; S, 14.92. Found: C, 44.97; H, 6.65; N, 25.94; S, 14.99.

Reaction of 12 with NaN_3.—A mixture of **12** (2.56 g) and NaN_3 (0.75 g) in DMF (20 ml) was heated at *ca.* 130° until no more gas evolution was visible. The deep blue color disappeared; the DMF was stripped; and the residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ was dried and evaporated to give 0.67 g (43%) of crude 5-(dimethylamino)-3-(methylamino)-1,2,4-thiadiazole (**13**) as a light yellow oil that solidified in a distillation apparatus [105–110° (0.15 mm)]. Recrystallization from hexane–EtOAc gave the pure material, mp 77–79°.

Anal. Calcd for $C_5H_{10}N_4S$: C, 37.95; H, 6.37; N, 35.41. Found: C, 37.91; H, 6.16; N, 35.67.

The structural assignment (**13** as opposed to the other possible isomer) is made partly by analogy to the formation of **15** from **14** (*vide infra*) and also by a strong peak in the mass spectrum at *m/e* 88 [$Me_2NC(=S)^+$].

Reaction of 14 with NaN_3.—A mixture of **14** (7.27 g) and NaN_3 (2.09 g) in DMF (40 ml) was heated at reflux 20 min (only a yellow color developed in this case). The solvent was stripped and the residue was extracted with several portions of warm MeOH; these extracts were filtered and evaporated and the remaining solid was washed with water and dried to give 2.44 g (56%) of 3-amino-5-(dimethylamino)-1,2,4-thiadiazole (**15**), mp 225–227.5°. An analytical sample was recrystallized from absolute ethanol, mp 230–232°.

Anal. Calcd for $C_4H_8N_4S$: C, 33.31; H, 5.58; N, 38.86; S, 22.24. Found: C, 33.43; H, 5.63; N, 39.01; S, 21.98.

(12) M. Ahmed and D. M. McKinnon, *Can. J. Chem.*, **48**, 2142 (1970).

(13) J.-L. Derocque and J. Vialle, *Bull. Soc. Chim. Fr.*, 1183 (1966).

The nmr spectrum (DMSO-d_6) was consistent with an amino(dimethylamino)thiadiazole [δ 3.00 (s, 6) and 5.98 (s, 2, exchangeable)] as was the mass spectrum (*m/e* 144). The opposite isomer, 5-amino-3-(dimethylamino)-1,2,4-thiadiazole, has been reported[14] to have mp 161°.

Reaction of 16 with NaN_3.—A mixture of **16** (1.00 g) and NaN_3 (0.269 g) in DMF (28 ml) was refluxed 45 min. The DMF was stripped and the residue was partitioned between benzene and water. The benzene solution was dried and evaporated leaving 0.380 g of an oily tan solid that was extracted with several small portions of MeOH (to remove sulfur). Treatment of the MeOH solution with water precipitated a light tan solid, mp 88–90°, that was again taken up in MeOH to remove a little more sulfur. Evaporation of the MeOH and recrystallization of the residue from hexane gave 0.153 g (24%) of 5-(dimethylamino)-3-phenyl-1,2,4-thiadiazole (**17**), mp 89–90° (reported[7] mp 89°).

Registry No.—**9**, 31354-27-5; **9′**, 31354-28-6; **10**, 31354-29-7; **11**, 31354-30-0; **12**, 31354-31-1; **13**, 31354-32-2; **14**, 31354-33-3; **15**, 31354-34-4; **16**, 31354-35-5; NaN_3, 12136-89-9; 3,5-dipiperidino-1,2,4-dithiazolium bromide, 31354-36-6; 3,5-dipiperidino-1,2,4-thiadiazole, 31354-37-7.

Acknowledgment.—We thank Miss Barbara Bierl for the mass spectra and Mr. R. T. Brown for the preparation of some starting materials.

(14) J. Goerdeler and M. Willig, *Chem. Ber.*, **88**, 1071 (1955).

Preparation of 2-Alkoxyiminoalkyl Bromides by the Bromination of *O*-Alkyl Oximes with *N*-Bromosuccinimide[1]

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Received April 30, 1971

Several methods are available for the preparation α-halo ketoximes and α-halo aldoximes; these include the reduction of nitro olefins with zinc chloride,[3] the reaction of an olefin with nitrosyl chloride,[4] and the direct oximation of α-halocarbonyls.[5] Reactions of these compounds with certain nucleophiles have also been explored.[3,6] The corresponding *O*-alkyl ethers, however, have not been described.

N-Bromosuccinimide (NBS) can be used to brominate various types of compounds[7] including cyclohexanone and cyclopentanone oximes which yield the

(1) This investigation was supported by U. S. Public Health Service Research Grant RH 00293, National Center for Radiological Health.

(2) Abstracted from the Ph.D. dissertation, University of Illinois at the Medical Center, 1970.

(3) A. Dornow, H. D. Jordan, and A. Muller, *Chem. Ber.*, **94**, 67 (1961).

(4) (a) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 369 (1951); (b) M. Ohno, N. Naruse, S. Torimitsu, and M. Okamoto, *Bull. Chem. Soc. Jap.*, **39**, 1119 (1966).

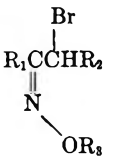
(5) E. T. Bailey, Ph.D. Thesis, University of Illinois, 1965.

(6) (a) A. Dornow and H. D. Jordan, *Chem. Ber.*, **94**, 76 (1961); (b) A. Dornow, H. H. Marquardt, and H. Pauckseh, *ibid.*, **97**, 2165 (1964); (c) M. Ohno and N. Naruse, *Bull. Chem. Soc. Jap.*, **39**, 1125 (1966); (d) M. Ohno, S. Torimitsu, N. Naruse, M. Okamoto, and I. Sakai, *ibid.*, **39**, 1129 (1966); (e) M. Masaki, M. Sugiyama, S. Tayama, and M. Ohta, *ibid.*, **39**, 2745 (1966).

(7) (a) L. Horner and E. H. Winklemann in "Newer Methods of Preparative Organic Chemistry," Vol. III, W. Foerst, Ed., Academic Press, New York, N. Y., 1964, p 151; (b) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

TABLE I

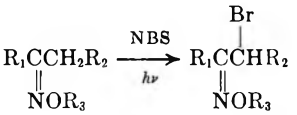
ALKOXYIMINOALKYL BROMIDES PREPARED BY NBS BROMINATION OF *O*-ALKYL OXIMES



Compd	R_1	R_2	R_3	Yield, %	Bp, °C (mm)	Refractive index	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Br, % Calcd	Br, % Found
1	Me	H	Et	32	54–57 (10)	n^{20}D 1.4764	33.35	33 48	5.60	5 55	7.78	7 93	44.38	44.57
2	Me	Me	Et	71	65–68 (12)	n^{25}D 1.4700	37.13	37.35	6.23	6.46	7.22	7.32	41.17	40.97
3	H	Et	Et	71	60–62 (7)	n^{20}D 1.4696	37.13	37.30	6.23	6.41	7.22	7.38	41.17	41.06
4	Me	Et	Et	61	92–94 (42)	n^{23}D 1.4721	40.40	40.49	6.78	6 71	6.73	6.70	38.40	38.36
5	Ph	H	Et	41	76.5–79 (0.02)	n^{16}D 1.5705	49.61	*a*	5.00	*a*	5.70	*a*	33.00	*a*
6	Me	Ph	Et	40	77–79 (0.04)	n^{26}D 1.5455	51.58	51 46	5 51	5.55	5.47	5.45	31.20	31.44
7	Me	H	Me	54	52–53 (31)	n^{21}D 1.4825	28.94	28.93	4.86	5.06	8 44	8 32	48.13	48.40
8	Me	Me	Me	73	64–65 (40)	n^{23}D 1.4726	33.35	33.44	5.60	5.81	7.78	7.81	44.38	44.63
9	H	Et	Me	30	76–78 (40)	$n^{23.5}$D 1.4756	37.13	37.20	6.23	6.19	7.22	7.29	41 17	41.39
10	Me	Et	Me	79	62–64 (0.01)	n^{22}D 1.5813	47.39	47.42	4.42	4.49	6.14	6.14	35.03	35.30
11	Ph	H	Me	70	66–68 (37)	n^{20}D 1.4687	33.35	33.50	5.60	5.62	7.78	7.70	44 38	44.55
12	$-(CH_2)_3-$		Et	47	50–52 (0.01)	n^{20}D 1.5077	40.80	40.71	5.87	5 91	6.80	6 95	38 77	38.56
13	$-(CH_2)_4-$		Et	73	52–56 (0.02–0.03)	n^{26}D 1.5110	43.65	43.64	6 41	6.50	6.36	6.52	36.30	36.44
14	$-(CH_2)_3-$		Me	58	50–52 (0.06)[b]	n^{24}D 1.5162	37.52	37.56	5.25	5.38	7.29	7.26	41.61	41.60

[a] The elemental analysis was not satisfactory. The compound was identified by two solid derivatives, namely sodium *S*-(2-ethoxyimino-2-phenylethyl) thiosulfate [*Anal.* Calcd. for $C_{10}H_{16}NNaO_5S_2$ (monohydrate): C, 29.89; H, 5.73; N, 4.98; S, 22.79. Found: C, 30.04; H, 5.81; N, 5.11; S, 22.73.] and 2-(2-ethoxyimino-2-phenylethylthio)-2-imidazolinium bromide, mp 133–135° (*Anal.* Calcd for $C_{13}H_{18}BrN_3OS$: C, 45.35; H, 5.27; N, 12.21; S, 9.31. Found: C, 45.41; H, 5.39; N, 12.27; S, 9.30). Attempts were made to purify the compound by chromatography on a silica column (eluting solvent, petroleum ether–$CHCl_3$ 1.3:1) and by preparative thin layer chromatography (silica gel GF-254 plates, mixture of 90 ml of petroleum ether and 70 ml of $CHCl_3$ as developing solvent). The major fraction yielded a light yellow liquid after evaporation of solvent: mass spectrum (70 eV) *m/e* 241, 243 (M^+). The nmr spectrum ($CDCl_3$) showed no bands that did not satisfy the proposed structure nor were the integrals unreasonable. The elemental analysis, however, was not satisfactory. [b] A second product, bp 70–72° (0.06 mm), n^{24}D 1.5575, was analyzed for the dibromo derivative. It has tentatively been assigned the symmetrical structure 2,5-dibromocyclopentanone oxime *O*-methyl ether: nmr spectrum (CCl_4) δ 2.00–2.87 (m, 44), 4.06 (s, 3 H), 4.86–5.17 [two broad bands, 2 H, $(CHBr)_2C{=}N$]. *Anal.* Calcd for $C_6H_9Br_2NO$: C, 26.60; H, 3.35; N, 5.17; Br, 58.98. Found: C, 26.74; H, 3.49; N, 5.34; Br, 58.87.

corresponding α-bromonitrosoalkanes.[8] In this investigation, it was found that *O*-alkyl (methyl or ethyl) ethers of ketoximes or aldoximes react readily with NBS to form the title compounds (Table I) in yields up to 79%.



The reaction was carried out by mixing equimolar quantities of the oxime ethers and pulverized *N*-bromosuccinimide in carbon tetrachloride. The mixture was heated at reflux with the introduction of radiant energy from an ultraviolet sun lamp (GE, 275 W). Preliminary work to determine optimum conditions was carried out utilizing butanone oxime *O*-ethyl ether. It was found that heat alone was unsatisfactory since the reaction time was protracted. Photoactivation by a sunlamp was found superior to dibenzoyl peroxide as an initiator. A combination of both proved to have little advantage over photoactivation alone.

While bromination of methyl and ethyl ethers proceeded without attack on the *O*-alkyl group, butanone oxime *O*-benzyl ether produced an intractable oil which showed that the benzylic carbon had been brominated [nmr δ 9.95 (CCl_4)]. When the mixture was treated with sodium bicarbonate, benzaldehyde was detected by nmr [δ 9.93 (CCl_4)] and its characteristic odor.

Experimental Section

The melting points and boiling points recorded are uncorrected. Melting points were taken on a Thomas-Hoover capillary melting point apparatus. Refractive indices were determined on a Bausch and Lomb Abbe 3L refractometer. Elemental Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland, and by Micro-Tech Laboratories, Inc., Skokie, Ill. The nmr spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as internal reference. The mass spectra were obtained from a Hitachi Perkin-Elmer RMU-60 mass spectrometer.

Materials.—The oximes, ketones, and *N*-bromosuccimide were obtained from commercial sources (Eastman Organic Chemicals, Matheson Coleman and Bell) and were used without further purification. 2-Pentanone oxime, bp 90–93° (33 mm) with n^{20}D 1.4452 (lit.[9] bp 167°, n^{20}D 1.44546), and phenyl-2-propanone oxime, mp 67–69° (petroleum ether) (lit.[10] mp 68–70°), were prepared by a standard method.[11a] Cyclohexanone oxime was prepared according to a known procedure,[11b] mp 88–90° (lit.[11b] mp 89–90°).

The following *O*-alkyl oximes were prepared by alkylating oximes using methyl sulfate or ethyl sulfate according to known procedures:[12] acetone oxime *O*-ethyl ether, bp 92–94°, n^{20}D 1.4040 (lit.[9] bp 93°, n^{20}D 1.4042); butanone oxime *O*-ethyl ether, 113–115°, n^{20}D 1.4128 (lit.[9] bp 113°, n^{20}D 1.4115); 2-pentanone oxime *O*-ethyl ether, bp 132–136°, n^{21}D 1.4181 [lit.[9] bp 134° (754 mm), n^{20}D 1.41836]; cyclohexanone oxime *O*-ethyl ether, bp 72–74° (13–15 mm), n^{16}D 1.4630 [lit.[12a] bp 70° (14 mm), n^{20}D 1.46327]; acetone oxime *O*-methyl ether, bp 68–71°, n^{25}D 1.3971 (lit.[9] bp 73°, n^{20}D 1.40052); butanone oxime *O*-methyl ether, bp 90–94°, $n^{23.5}$D 1.4092 [lit.[12b] bp 66° (301 mm), n^{20}D 1.4099]; acetophenone oxime *O*-methyl ether, bp 89–92° (8 mm), n^{23}D 1.5414 [lit.[12b] bp 73–74° (2.2 mm), n^{20}D 1.5415]; cyclopentanone oxime *O*-methyl ether, bp 50–53° (40 mm), n^{29}D 1.4524 [lit.[12b] bp 36° (10 mm), n^{20}D 1.4560]; acetophenone oxime *O*-ethyl ether,

(8) D. C. Iffland and G. X. Criner, *J. Amer. Chem. Soc.*, **75**, 4047 (1953).

(9) A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *J. Chem. Soc.*, 514 (1952).

(10) G. Harris, Ed., "Dictionary of Organic Compounds," Vol. 4, Oxford University Press, New York, N. Y., 1965, p 2715.

(11) (a) A. H. Blatt, Ed., "Organic Syntheses," Collect Vol. II, McGraw-Hill, New York, N. Y., 1943, p 313; (b) R. Adams and J. R. Johnson, "Laboratory Experiments in Organic Chemistry," 4th ed, Macmillan, New York, N. Y., 1949.

(12) (a) M. Hudlicky and J. Hokr, *Collect. Czech. Chem. Commun.*, **14**, 561 (1949); (b) A. Reiser, V. Jehlicka, and K. Dvorak, *ibid.*, **16**, 13 (1951).

bp 50–53° (0.04 mm), $n^{20}D$ 1.5322 [lit.[13] bp 130–135° (20 mm)[14]]; cyclopentanone oxime *O*-ethyl ether reported[15] without physical constants, bp 59–61° (15–16 mm), $n^{20}D$ 1.4540, was analyzed for $C_7H_{13}NO$ (Calcd: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.28; H, 10.14; N, 11.11). Previously unreported oxime ethers included *n*-butyraldoxime *O*-ethyl ether, bp 119–121°, $n^{14}D$ 1.4133 (*Anal.* Calcd for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.63; H, 11.34; N, 12.19); *n*-butyraldoxime *O*-methyl ether, bp 93–97°, $n^{25}D$ 1.4054 (*Anal.* Calcd for $C_5H_{11}NO$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.52; H, 10.82; N, 13.94); phenyl-2-propanone oxime *O*-ethyl ether, bp 60–66° (0.01–0.1 mm) $n^{21}D$ 1.5070 (*Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.53; H, 8.62; N, 8.02); 2-pentanone oxime *O*-methyl ether, bp 118–120°, $n^{24}D$ 1.4152 (*Anal.* Calcd for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.68; H, 11.30; N, 12.12).

General Procedure for the NBS Bromination of *O*-Alkyl Oximes.—The procedure for the preparation of 3-bromo-2-butanone oxime *O*-methyl ether is representative. A mixture of 20.2 g (0.2 mol) of 2-butanone oxime *O*-methyl ether and 35.6 g (0.2 mol) of *N*-bromosuccinimide in 80 ml of carbon tetrachloride was heated at reflux with occasional shaking and irradiated with a 275-W G.E. sunlamp (about 10 cm away). In about 15 min, vigorous boiling ensued with the development of an intense red-dish-brown color and, after an additional 10 min, the color suddenly disappeared and the boiling subsided. The reaction mixture was cooled and filtered with suction, and the residue was washed with a small amount of carbon tetrachloride. The filtrate was combined with the washings and then shaken with 50 ml of a saturated solution of sodium bicarbonate. The organic layer was dried (Na_2SO_4) and distilled under diminished pressure to remove the solvent. The residual yellow liquid was then distilled twice under reduced pressure giving 26.2 g (72.8%) of **8**. Physical properties, spectral data, and elemental analysis are shown in Tables I and II.

TABLE II

NMR DATA OF 2-ALKOXYIMINOALKYL BROMIDES

Compd	Solvent	Nmr, δ
1	Neat	1.20 (t, 3, J = 7.0 Hz), 1.88 (s, 3), 3.90 (s, 2), 4.04 (q, 2, J = 7.0 Hz)
2	$CDCl_3$	1.23 (t, 3, J = 7.0 Hz), 1.78 (d, 3, J = 7.0 Hz), 1.92 (s, 3), 4.09 (q, 2, J = 7.0 Hz), 4.70 (q, 1, J = 7.0 Hz)
3	Neat	1.00 (t, 3, J = 7.0 Hz), 1.17 (t, 3, J = 7.0 Hz), 1.72–2.27 (m, 2), 4.03 and 4.09 (two q, 2, J = 7.0 Hz), 4.45 and 5.00 (two q, with ratio of 3 to 1, 1, $J \simeq$ 7.5 Hz, CHBr), 6.70 and 7.35 (two d, with ratio of 1 to 3, J = 8.8 Hz)
4	$CDCl_3$	0.98 (t, 3, J = 7.0 Hz), 1.23 (t, 3, J = 7.0 Hz), 1.90 (s, 3) 1.70–2.35 (m, 2), 4.13 (q, 2, J = 7.0 Hz), 4.52 (t, 1, $J \simeq$ 7.5 Hz)
5	$CDCl_3$	1.36 (t, 3, J = 7.0 Hz), 4.37 (q, 2, J = 7.0 Hz, 4.38 (s, 2), 7.30–7.90 (m, 5)
6	CCl_4	1.22 (t, 3, J = 7.0 Hz), 1.87 (s, 3), 4.12 (q, 2, J = 7.0 Hz), 5.80 (s, 1), 7.18–7.61 (m, 5)
7	$CDCl_3$	1.96 (s, 3), 3.90 (s, 3), 3.99 (s, 2)
8	$CDCl_3$	1.81 (d, 3, J = 7.0 Hz), 1.93 (s, 3), 3.89 (s, 3), 4.77 (q, 1, J = 7.0 Hz)
9	CCl_4	1.83–2.67 (m, 6), 3.86 (s, 3), 4.80–5.00 (m, 1)
10	$CDCl_3$	1.01 (t, 3, J = 7.0 Hz), 1.76–2.20 (m, 2), 1.89 (s, 3), 3.85 (s, 3), 4.47 (t, 1, $J \simeq$ 7.5 Hz)
11	$CDCl_3$	4.04 (s, 3), 4.29 (s, 2), 7.22–7.84 (m, 5)
12	Neat	1.29 (t, 3, J = 7.0 Hz), 1.80–3.00 (m, 6), 4.36 (q, 2), 5.18–5.38 (one broad band, 1)
13	Neat	1.29 (t, 3, J = 7.0 Hz), 1.25–3.60 (m, 8), 4.31 (q, 2), 5.17–5.40 and 5.85–6.10 (two broad bands, 1)
14	CCl_4	1.83–2.67 (m, 6), 3.86 (s, 3), 4.80–5.00 (m, 1)

Registry No.—**1**, 31376-82-6; **2**, 31376-83-7; **3**, 31376-84-8; **4**, 31376-85-9; **5**, 31376-86-0; **6**, 31376-87-1; **7**, 31376-88-2; **8**, 31376-89-3; **9**, 31376-90-6; **10**, 31376-91-7; **11**, 31376-92-8; **12**, 31376-93-9; **13**, 31376-94-0; **14**, 31376-95-1; cyclopentanone oxime *O*-ethyl ether, 31376-96-2; *n*-butyraldoxime *O*-ethyl ether, 20135-03-9; *n*-butyraldoxime *O*-methyl ether, 31376-98-4; phenyl-2-propanone oxime *O*-ethyl ether, 31376-99-5; 2-pentanone oxime *O*-methyl ether, 31377-00-1; sodium *S*-(2-ethoxyimino-2-phenylethyl) thiosulfate, 31377-01-2; 2-(2-ethoxyimino-2-phenylethylthio)-2-imidazolinium bromide, 31377-02-3; 2,5-dibromocyclopentanone oxime *O*-methyl ether, 31377-03-4; NBS, 128-08-5.

(13) W. R. Dunstan and E. Goulding, *J. Chem. Soc.*, **79**, 628 (1901).

(14) The refractive index of this compound was not reported, therefore its structure was confirmed by nmr (neat TMS internal standard): δ 1.27 (t, 3 H), 2.10 (s, 3 H), 4.21 (q, 2 H), 7.50–7.79 (m, 2 H), and 7.08–7.37 (m, 3 H).

(15) L. G. Donaruma, *J. Org. Chem.*, **22**, 1024 (1957).

Methylation of 2-Aminobenzimidazole

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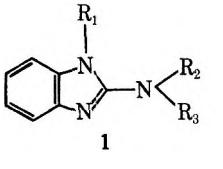
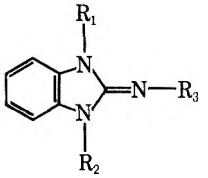
Received March 22, 1971

During an investigation of the preparation and properties of 2-aminobenzimidazoles, we wished to determine the nature of the products formed by direct methylation of these compounds. Methylation of 2-aminobenzimidazole can lead to either of two products, **1** and **2** ($R_1 = R_2 = R_3 = CH_3$). Based upon the observed behavior of the 5-aminotetrazoles,[2a] formation of the imine **2** was anticipated.



1



2

Treatment of 2-aminobenzimidazole with dimethyl sulfate afforded a trimethylated product whose physical properties differed substantially from those of an authentic sample of 1-methyl-2-dimethylaminobenzimidazole[2b] and which was apparently the expected 1,3-dimethyl-2-methyliminobenzimidazole. The ultraviolet spectrum of this compound shows only a single strong absorption at 284 nm rather than the two distinct maxima characteristic of both 2-aminobenzimid-

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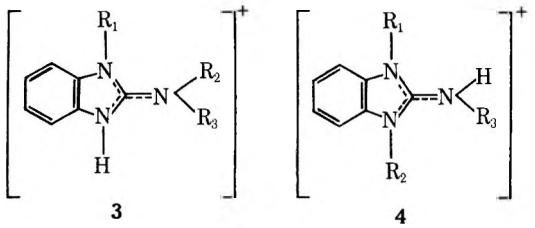
(2) (a) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Amer. Chem. Soc.*, **76**, 2894 (1954); D. B. Murphy and J. P. Picard, *J. Org. Chem.*, **19**, 1807 (1954). (b) A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **44**, 1273 (1961).

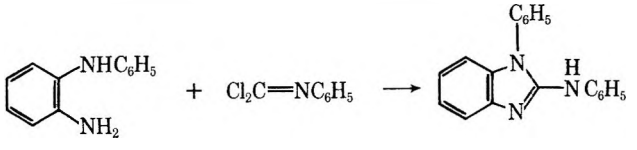
azole (244 and 283 nm) and 1-methyl-2-dimethylaminobenzimidazole (255 and 287 nm). The similarity in the spectra of the latter two compounds strongly suggests that 2-aminobenzimidazole exists principally in the form of the primary amine **1** rather than as the tautomeric imine **2** ($R_1 = R_2 = R_3 = H$).[3] When protonated, all three compound should exhibit guanidinium-type resonance (**3** and **4**) and, as expected, they show similar absorption in acid solution.



3 **4**

2-Anilinobenzimidazole also undergoes methylation of both ring nitrogens, yielding 1,3-dimethyl-2-phenyliminobenzimidazole, as evidenced by the higher melting point, more complex uv spectrum, and completely different ir spectrum, compared with those of authentic 1-methyl-2-(*N*-methylanilino)benzimidazole.[2b] Again, the differences in the uv spectrum largely disappear in acid solution.

In the course of this work, the previously unreported compound 1-phenyl-2-anilinobenzimidazole was prepared by the reaction of *N*-phenyl-*o*-phenylenediamine with phenyl carbonimidoyl dichloride.



Experimental Section[4]

2-Aminobenzimidazole.—A mixture of 0.24 g of benzimidazole-2-sulfonic acid[5] and 1 ml of 28% aqueous NH_3 was heated in a sealed tube at 160° for 6 hr. After recrystallization from alcohol and water, the product melted at 222° (lit.[6] 222°): λ_{max}^{EtOH} 244 nm (ε 6300), 283 (7950); $\lambda_{max}^{0.1\ N\ HCl}$ 276 nm (ε 9200).

1-Methyl-2-dimethylaminobenzimidazole.—A mixture of 0.2 g of 1-methyl-2-chlorobenzimidazole[2b] and 1.6 ml of 3.7 *N* dimethylamine in ethanol was heated 4 hr in a sealed tube at 150°. The mixture was evaporated, treated with Na_2CO_3 solution, and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and treated with a solution of dry HCl in $CHCl_3$. Chilling afforded crystals of the hydrochloride: mp 236–238° (lit.[2b] 238–239); $\lambda_{max}^{0.1\ N\ NaOH}$ 250 nm (ε 7500), 255 (7550), 287 (9800); $\lambda_{max}^{0.1\ N\ HCl}$ 281 nm (ε 9250), 288 (9400); ir (Nujol) 6.08, 12.2, 12.95, 13.1 μ.

1-Methyl-2-(*N*-methylanilino)benzimidazole was prepared in 43% yield by heating 0.214 g of redistilled *N*-methylaniline, 0.64 g of 22% BuLi in hexane, and 0.200 g of 1-methyl-2-chlorobenzimidazole under reflux in benzene for 2.5 hr. The solution was evaporated *in vacuo*, and the residue was taken up in ether. The ether solution was washed once with H_2O, dried ($MgSO_4$), and evaporated, leaving an oil which soon solidified. The crystals were sublimed *in vacuo* and then recrystallized from petroleum ether (bp 60–70°): mp 131–131.5° (lit.[2b] mp 128–129°); λ_{max}^{EtOH} 258 nm (ε 10,700), 294 (18,700); $\lambda_{max}^{0.1\ N\ HCl}$ 244 nm (ε 11,200), 288 (19,950); ir (Nujol) 6.22, 6.31, 6.58, 7.82, 8.06, 12.62, 13.22, 13.48, 13.78, 14.42 μ.

Methylation of 2-Aminobenzimidazoles.—Methylation was carried out according to the method described by Herbst, *et al.*, for the methylation of 1-ethyl-5-aminotetrazole.[7] From 0.133 g (0.001 mol) of 2-aminobenzimidazole and 0.441 g (0.0035 mol) of $(CH_3)_2SO_4$ was obtained 0.08 g of white, waxy crystals of 1,3-dimethyl-2-methyliminobenzimidazole, mp 62–64°, after purification by sublimation: λ_{max}^{EtOH} 250 nm (sh) (ε 10,700), 284 (22,800); $\lambda_{max}^{0.1\ N\ HCl}$ 277 nm (22,450), 283 (22,400).

Anal. Calcd for $C_{10}H_{12}N_3$: C, 68.57; H, 7.43. Found: C, 68.50, H, 7.40.

The hydrochloride melted at 253–255°: ir of hydrochloride (Nujol) 5.8, 5.9, 6.0, 13.4, 13.7 μ.

Treatment of 0.209 g (0.001 mol) of 2-anilinobenzimidazole[8] with 0.441 g (0.0035 mol) of $(CH_3)_2SO_4$ gave 0.18 g of 1,3-dimethyl-2-phenyliminobenzimidazole, which was recrystallized five times from EtOH–H_2O: mp 197–198°; λ_{max}^{EtOH} 247 nm (ε 16,600), 257 (20,000), 263 (21,000), 294 (28,700), 302 (30,500); $\lambda_{max}^{0.1\ N\ HCl}$ 246 nm (ε 17,200), 286 (25,000).

Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.95; H, 6.33; N, 17.72. Found: C, 75.64; H, 6.05; N, 17.67.

The hydrochloride melted at 235–237°: ir (Nujol) 6.25, 6.6 6.7, 8.1, 11.7 w, 13.0 w, 13.4 sh, 1.5 s, 14.4 μ.

1-Phenyl-2-anilinobenzimidazole.—To a solution of 2.76 g (0.015 mol) of *N*-phenyl-*o*-phenylenediamine in 25 ml of 1,2-dichloroethane was added 2.61 g (0.015 mol) of phenyl carbonimidoyl dichloride.[8] Crystals appeared after a short time, and after several days a total of 2.91 g (60%) of purple, matted crystals separated, mp 218°. After several recrystallizations from H_2O, the hydrochloride was obtained as white crystals, mp 236–240°.

Anal. Calcd for $C_{19}H_{16}N_3Cl$: C, 70.91; H, 5.02; N, 13.06. Found: C, 70.70; H, 5.13; N, 13.20.

Addition of dilute NaOH to a solution of the hydrochloride precipitated 1-phenyl-2-anilinobenzimidazole: mp 160–165°; λ_{max}^{EtOH} 302 nm (ε 22,600), 296 (22,950), 256 (20,225), 245 sh (18,600); $\lambda_{max}^{0.1\ N\ HCl}$ 285 (ε 21,250), 280 (20,875); ir (Nujol) 6.13, 6.22, 6.35, 13.5, 14.4 μ.

Registry No.—**1** ($R_1 = R_2 = R_3 = H$), 934-32-7; **1** ($R_1 = R_2 = R_3 = Me$), 6595-23-9; **1** ($R_1 = Me$; $R_2 = Ph$; $R_3 = Me$), 31413-78-2; **1** ($R_1 = Ph$; $R_2 = Ph$; $R_3 = H$) HCl, 31413-79-3; **1** ($R_1 = R_2 = Ph$; $R_3 = H$), 31413-80-6; **2** ($R_1 = R_2 = Me$; $R_3 = Ph$), 29290-31-1; **2** ($R_1 = R_2 = Me$; $R_3 = Ph$) HCl, 31413-82-8; **2** ($R_1 = R_2 = R_3 = Me$), 19363-66-7; **2** ($R_1 = R_2 = R_3 = Me$)·HCl, 31413-84-0.

(3) A. R. Katritzky and J. M. Lagowski in *Advan. Heterocycl. Chem.*, **2**, 71 (1963).

(4) Melting points were determined on a calibrated Thomas-Hoover apparatus. Ultraviolet spectra were obtained using a Bausch and Lomb Spectronic 505. The infrared spectra were determined as Nujol mulls, using a Perkin-Elmer 137 spectrophotometer. Microanalyses by Schwartzkopf Microanalytieal Laboratory, Woodside, N. Y.

(5) J. G. Everett, *J. Chem. Soc.*, 2406 (1930).

(6) I. G. Farbenindustrie, German Patent 612,544 (1935); *Chem. Abstr.*, **30**, 733 (1936).

(7) R. M. Herbst, C. W. Roberts, and E. J. Harvill, *J. Org. Chem.*, **16**, 139 (1951).

(8) D. B. Murphy, *ibid.*, **29**, 1613 (1964).

Isomeric Steroidal Isoxazolines by 1,3 Dipolar Cycloaddition

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Dipolar addition of nitrile oxides to unsaturated systems affords a simple method of preparing isoxazoline derivatives and has been used extensively to prepare 4,5-dihydro-1,2-oxazoles.[1] It was long believed that such cycloaddition to an asymmetric ene system resulted in only one of the two possible isomers, namely that in which the oxygen of the nitrile oxide is bonded to the

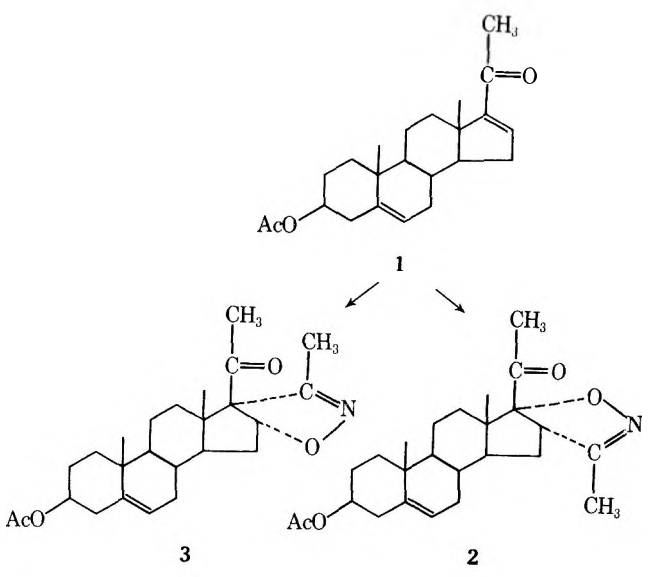
(1) C. Grundmann and P. Grünanger, "Nitrile Oxides," Springer Verlag, New York, N. Y., and Heidelberg, 1971.

most heavily substituted carbon atom of the asymmetric double bond ("normal addition"). Recently, however, a few instances in which the other possible isomer (arising from "inverse addition") was also formed have been reported.[2,3]

This "inverse" addition has been interpreted by Huisgen[4a] as arising from a concerted dipolar mechanism as a consequence of the steric requirements of a four-center intermediate, or, alternatively, from an inversion of the polarity of the dipole or of the dipolarophile. Firestone, however, suggests that it is due to a biradical mechanism, and the relative merits of these two mechanisms have been discussed in the literature.[4b,c]

The general biological interest in the steroidal adducts of the isoxazoline type is evident by the number of reported syntheses by 1,3 dipolar addition,[5] and recently we have been studying the addition of nitrile oxides to ene steroidal systems; the results of such addition to 20-oxopregna-5,16-dien-3β-yl acetate (**1**) is reported here.

This reaction has been studied by Culbertson, *et al.*,[5a] and they reported only one reaction product (**2**) derived from "normal" addition of the CH_3CNO to the C_{16}–C_{17} double bond, whereas we have isolated also another isomer arising from "inverse" addition (**3**).



Experimental Section

Melting points were obtained using a Kofler hot-plate microscope and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer using the Nujol mull technique. Proton nmr spectra were recorded on a Perkin-Elmer R12 spectrometer at 60 MHz, and the reported chemical shifts are on the δ scale in parts per million downfield from internal TMS. Mass spectra were obtained using a Perkin-Elmer 270 mass spectrometer, the potential being 80 ev, and the samples were directly introduced at 200°. The specific rotations were measured with a Perkin-Elmer 141 polarimeter.

Optical rotatory dispersion curves and uv spectra were obtained using a Jasco ORD/UV-5 spectrometer, and circular dichroism curves with a Cary 60 spectrometer. The uv data for dioxane solutions were obtained using a Beckman DU2 spectrometer. The purity of the products was determined at each stage by tlc on silica gel G using the eluent systems *n*-hexane–acetone (3:1) and chloroform–ethyl acetate–*n*-hexane (94:5:1).

Acetylhydroxamoyl Chloride.—The method of Casnati and Ricca[6] was used but modified to reduce risk of explosion by using chloroform as solvent.

Addition of Acetonitrile Oxide to 20-Oxopregna-5,16-dien-3β-yl Acetate (1).—A solution of 90 ml of triethylamine in 850 ml of dry ethyl ether was added to 10 g of **1** and 8 g of acetylhydroxamoyl chloride in 800 ml of dry ether over a period of 15 hr at room temperature. The ethereal solution was then dried (Na_2SO_4) and evaporated to dryness. Recrystallization of the crude reaction product from methanol yielded a mixture of the two isomers **2** and **3**, with physical-chemical data reported by Culbertson, *et al.*[5a]

Tlc of the crude reaction product, however, showed the presence of three compounds, the two isomeric adducts (of closely comparable R_f value) and dimethylfuroxan (4,5-dimethyl-1,2,5-oxadiazole *N*-oxide).

These were separated by column chromatography on a column, 7-cm inner diameter, 80-cm height, containing 1800 g of silica gel–Celite 535 (1:1), activated for 1 hr at 110° and eluted first with petroleum ether to remove dimethylfuroxan and then with *n*-hexane–acetone (98:2) to separate the two isomeric adducts. After recrystallization from methanol these gave the following physiochemical characteristics.

Isomer 2: mp 243–244°; $[\alpha]^{20}D$ +22° (*c* 0.5, dioxane); ir 1730, 1710, 1635, 1245 cm^{-1}; ORD (*c* 5.0 mg/ml, dioxane, 390–250 mμ) $[\Phi]_{390}$ +990°, $[\Phi]_{323}$ +8680°, $[\Phi]_{301}$ ±0°, $[\Phi]_{276-279}$ −9760°, $[\Phi]_{250}$ −6120°; CD (*c* 4.98 mg/ml, dioxane, 335–250 mμ) $[\theta]_{335}$ ±0°, $[\theta]_{304-305}$ +14,870°, $[\theta]_{299}$ +16,030°, $[\theta]_{250}$ +580°; uv max 291 mμ (ε 145); nmr ($CDCl_3$) δ 0.71 (s, 3, 18-CH_3), 1.02 (s, 3, 19-CH_3), 1.91 (s, 3, 3-CH_3 isoxazoline), 2.05 (s, 3, 3-OAc), 2.25 (s, 3, 21-CH_3), 3.84 (m, 1, 16-CH), 4.6 (m, 1, 3-CH), 5.4 (m, 1, 6-CH); mass spectrum *m/e* (rel intensity) 372 (2), 371 (14), 370 (55), 355 (1), 354 (8), 353 (33), 343 (0.5), 342 (1.5), 312 (3), 311 (13), 310 (60), 105 (19), 91 (21), 81 (25), 68 (100), 57 (22), 55 (28), 43 (60), 41 (24).

Anal. Calcd for $C_{25}H_{35}NO_4$: C, 72.61; H, 8.53; N, 3.39. Found: C, 72.54; H, 8.60; N, 3.35.

Isomer 3: mp 190–191°; $[\alpha]^{20}D$ +235° (*c* 0.51, dioxane); ir 1730, 1715, 1625, 1255 cm^{-1}; ORD (*c* 5.0 mg/ml, dioxane, 400–270 mμ) $[\Phi]_{400}$ +4130°, $[\Phi]_{330}$ +28,530°, $[\Phi]_{324}$ +25,230°, $[\Phi]_{320}$ + 26,050°, $[\Phi]_{306}$ ±0°, $[\Phi]_{276-278}$ −33,500°, $[\Phi]_{270}$ −32,670°; CD (c 4.58 mg/ml, dioxane, 345–247 mμ) $[\theta]_{345}$ ±0°, $[\theta]_{314}$ +40,540°, $[\theta]_{312}$ +40,270°, $[\theta]_{305}$ +45,870°, $[\theta]_{266}$ ±0°; uv max 235 mμ (ε 2100) and 304 (205); nmr ($CDCl_3$) δ 0.83 (s, 3, 18-CH_3), 1.02 (s, 3, 19-CH_3), 2.01 (s, 3, 3-CH_3 isoxazoline), 2.05 (s, 3, 3-OAc), 2.25 (s, 3, 21-CH_3), 4.6 (m, 1, 3-CH), 5.4 (m, 2, 6-CH and 16-CH); mass spectrum *m/e* (rel intensity) 413 (0.5), 398 (0.5), 370 (0.5), 355 (0.5), 354 (4), 353 (17), 352 (0.5), 339 (1), 338 (4), 336 (0.5), 335 (0.5), 326 (0.5), 312 (0.5), 311 (1), 310 (2), 229 (19), 228 (100), 215 (16), 214 (18), 213 (37), 145 (25), 143 (20), 139 (16), 126 (40), 120 (20), 108 (18), 107 (15), 105 (27), 91 (26), 81 (22), 43 (92), 41 (20).

Anal. Calcd for $C_{25}H_{35}NO_4$: C, 72.61; H, 8.53; N, 3.39. Found: C, 72.61; H, 8.59; N, 3.43.

Results and Discussion

Comparison of the ir spectra of **1**, **2**, and **3** shows that on adduct formation the double bond between C_{16} and C_{17} is removed. The absorption at 1590 cm^{-1} in **1**, due to the conjugation of the carbonyl group with the double bond, disappears on adduct formation and the removal of this conjugation is also indicated by the shift in the carbonyl frequency from 1670 cm^{-1} in **1** to 1710 cm^{-1} in **2** and 1715 cm^{-1} in **3**. Further confirmation of the new ring formation is the appearance of the weak absorption at 1635 cm^{-1} in **2** and 1615 cm^{-1} in **3**, attributable to vibration of the isoxazoline ring,[5a,b]

(2) M. Christl and R. Huisgen, *Tetrahedron Lett.*, 5209 (1968).

(3) P. Grünanger, personal communication.

(4) (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963); (b) R. A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968); (c) R. Huisgen, *ibid.*, **33**, 2291 (1968).

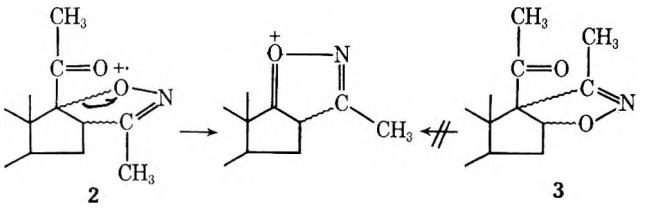
(5) (a) T. P. Culbertson, G. W. Moersch, and W. A. Neuklis, *J. Heterocycl. Chem.*, **1**, 280 (1964); (b) W. Fritsch, G. Seidl, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **677**, 139 (1964); (c) U. Stache, W. Fritsch, and H. Ruschig, *ibid.*, **685**, 228 (1965); (d) G. W. Moersch, E. L. Wittle, and W. A. Neuklis, *J. Org. Chem.*, **30**, 1272 (1965); (e) *ibid.*, **32**, 1387 (1967).

(6) G. Casnati and A. Ricca, *Tetrahedron Lett.*, 327 (1967).

and also by the disappearance of the band of **1** at 240 mμ in the ultraviolet spectrum.[5a]

That the isoxazoline rings formed have differing substitution patterns is indicated by their nmr spectra. That of **2** has signals at δ 3.84, attributable to the proton on C_{16} (*i.e.*, in position 4 of the isoxazoline ring), and at δ 5.4, both of integrated intensity one, whereas the spectrum of **3** has a signal at δ 5.4 of intensity two, due to the protons on C_6 and C_{16} (*i.e.*, position 5 of the isoxazoline ring), but no signal at δ 3.48.[7,8] The results can only be explained by the fact that during the reaction the oxygen of the reactant attaches to both C_{17} and C_{16} of the steroid to form two different isoxazoline rings.

Further evidence of this is the results of the mass spectra study. While the relative abundance of the mass peaks due to M − CH_3CO and M − CH_3CO_2H − CH_3CO in the spectrum of compound **2** can be easily

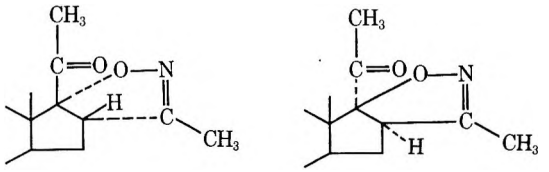


2 **3**

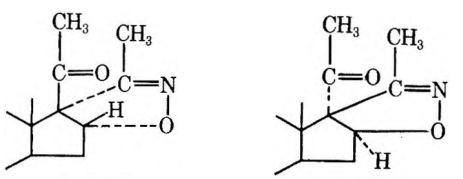
rationalized,[9] the analogous mechanism cannot arise from the structure (**3**), thus giving confirmation to the structures assigned to the two isomers.

However, while the addition of nitrile oxides to ene systems leads to isoxazoline rings of the substitution pattern shown, there still remains in this case the stereospecificity of the addition. While the cis stereospecificity of the addition necessarily restricts the number of possible configurations,[1,4a] there still remains two for each isomer, namely 16α,17α (**2** and **3**) or 16β, 17β (**2a** and **3a**) addition.

Here **2** and **3** have the acetyl group on C_{17} β and **2a** and **3a** have the acetyl group α. The configuration of



2 **2a**



3 **3a**

the acetyl side chain in position 17 has been determined by ORD and CD studies.

In studies of compounds of similar structures it has been found that if the acetyl group on C_{17} in steroids is β, the ORD curves and CD generally show a positive Cotton effect, attributable to the n → π* transition of the carbonyl group at C_{20}, whereas for an α orientation the Cotton effect is negative.[10a-d] We attribute the absorptions at 291 mμ for **2** and 304 mμ for **3** to n → π* transitions of the carbonyl groups. Besides, within the wavelength range of our study, no Cotton effect attributable to the >C=N- chromophore of the isoxazoline ring has been reported.[10d,e] Since both isomers exhibit strong positive Cotton effects at these frequencies (especially **3**), we thus conclude that the configuration of the acetyl group at C_{17} is β, so that attachment occurs α–α at C_{16}–C_{17} to form the isoxazoline ring.

That the values of the molecular ellipticity, molecular rotation, and the bathocromic shift of the Cotton effect due to the isoxazoline ring in compound **3** compared with the values obtained for 20-oxopregn-5-en-3β-yl acetate again gives confirmation to the assigned structures of the products. In **3** the >C=N- group is β–γ with respect to the C_{20} carbonyl, whereas in **2** it is γ–δ, and the higher values of molecular ellipticity and molecular rotation of the isomer assigned the structure **3** is in accord with reported data for β–γ unsaturated carbonyl systems.[11,12] The spectra also show some fine structure, especially that of **3**, as is generally found when the chromophore is conjugated or partially conjugated.

These proposed structures are also supported by the uv spectra. The spectra of the isomer given the structure **2** are very similar to that of the 20-oxopregn-5-en-3β-yl acetate, whereas the isomer given the structure **3** shows a bathochromic shift with respect to 20-oxopregn-5-en-3β-yl acetate, in keeping with the β–γ unsaturation of the proposed structure.[13-17]

While we cannot absolutely exclude the possibility in our case of an overlap of an n → π* transition of the >C=N- group with that of the carbonyl group, this >C=N- transition, if it exists, most probably has a very small ε value.

In fact, in reported studies of >C=N-containing compounds the absorption maxima are at rather low wavelengths,[10e,18,19] and on the basis of their ε values we think they must be attributed to π → π* transitions of the >C=N- group.

In any case neither Cotton effects nor uv absorption bands at wavelengths above 220 mμ have been reported for nonconjugated oximes, while for conjugated oximes

(7) A. Perotti, G. Bianchi, and P. Grünanger, "Convegno sulle risonanze magnetiche," Pavia, 1966.

(8) M. C. Aversa, G. Cum, and M. Crisafulli, *Gazz. Chim. Ital.*, **96**, 1046 1966).

(9) A. M. Duffield and O. Buchardt, *Org. Mass Spectrom.*, **3**, 1043 (1970).

(10) (a) C. Djerassi, *Bull. Soc. Chim. Fr.*, 741 (1957); (b) W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961); (c) P. Crabbé, F. Mc Capra, F. Comer, and A. I. Scott, *Tetrahedron*, **20**, 2455 (1964); (d) G. Snatzke and J. Himmelreich, *Tetrahedron*, **23**, 4337 (1967); (e) P. Crabbé and L. Pinelo, *Chem. Ind. (London)*, 158 (1966).

(11) P. Sunder-Plassman, P. H. Nelson, P. H. Boyle, A. Cruz, J. Iriarte, P. Crabbé, J. A. Zderic, J. A. Edwards, and J. H. Fried, *J. Org. Chem.*, **34**, 3779 (1969).

(12) P. Crabbé, "Applications de la Dispersion Rotatoire Optique et du Dicroisme Circulaire Optique en Chimie Organique," Gauthier-Villars, Paris, 1968, p 492, and references cited therein.

(13) R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962).

(14) Z.-Y. Kyi and W. Wilson, *ibid.*, 798 (1953).

(15) H. C. Barany, E. A. Braude, and M. Pianka, *ibid.*, 1898 (1949).

(16) E. S. Stern and C. J. Timmons, "Electronic Absorption Spectroscopy in Organic Chemistry," E. Arnold, Ed., London, 1970, pp 41, 42, and references cited therein.

(17) C. N. R. Rao, "Ultra-violet and visible spectroscopy," Butterworths, London, 1967, pp 27, 28, and references cited therein.

(18) H. Ley and H. Wingchen, *Ber.*, **67**, 501 (1934).

(19) G. W. Perold, A. P. Steyn, and F. V. K. von Reiche, *J. Amer. Chem. Soc.*, **79**, 462 (1957).

the uv absorption and Cotton effect are in the region 230–240 mμ[14,15,18] and no absorption at longer wavelengths corresponding to n → π* transitions of the >C=N– group have been reported.

As well as the low intensity long wavelength bands which we have attributed to n → π* transitions of the carbonyl groups, our uv spectra also show for **3** a maximum at 235 mμ and for **2** a shoulder at approximately 220 mμ.

While it proved impossible to obtain the relative proportions of the two isomers formed from the chromatographic separation due to partial overlap of dimethylfuroxan, we have obtained the relative proportions from the nmr spectrum of the crude reaction product. Since both **2** and **3** contribute to the signal at δ 5.4 (in the ratio of 1:2) while only **2** contributes to the signal at δ 3.84, from the relative intensities of these two signals we calculated the product ratio of **2**:**3** as 9:1.

Registry No.—**1**, 979-02-2; **2**, 1057-99-4; **3**, 1253-19-6.

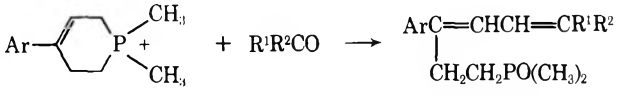
Preparation of 1,6-Diarylhexatrienes by a Modified Wittig Reaction

DANIEL LEDNICER

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

Received March 22, 1971

Recently we showed that reaction of cyclic phosphonium salts such as **1** with strong base followed by treatment of the resulting ylide with carbonyl compounds afforded a series of phosphorus-containing dienes.[1]



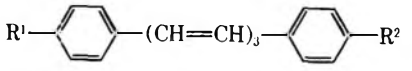
1 **2**

Prompted by the availability of a good method for the preparation of 1-methyl-3-phospholene,[2] we decided to investigate the behavior of the corresponding methiodide under the conditions of the Wittig reaction. Initial attempts to translate directly the reaction conditions used in the earlier work were not promising. When, however, a mixture of the salt and benzaldehyde was treated with 2 equiv of *tert*-butoxide in THF there was obtained on work-up an extremely insoluble crystalline compound. The absence of any PCH_3 bands in the nmr suggested that this was not a product analogous to **2**. The mass and uv spectra of the crude product both indicated this to be a mixture of isomeric 1,6-diphenylhexatrienes. Recrystallization afforded a pure sample of the polyolefin whose properties are in agreement with those recorded in the literature.[3]

(1) D. Lednicer, *J. Org. Chem.*, **35**, 2307 (1970).
(2) L. D. Quin and J. A. Peters, *Tetrahedron Lett.*, 3689 (1964).
(3) R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, **11**, 87 (1928).

By carefully adjusting conditions it proved possible to obtain this product in 26% yield by direct crystallization. Table I records results of this condensation employing several aldehydes.

TABLE I

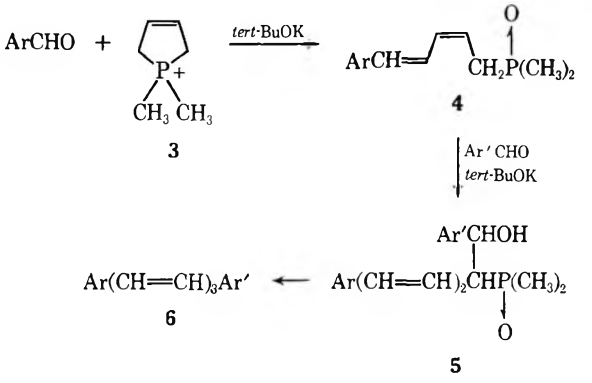


R¹	R²	Registry no.	Mp, °C	Lit mp, °C	Yield, %
H	H	1720-32-7	194–197	199–201[a]	26
CH_3	CH_3	31382-31-7	229–231		10[b]
OCH_3	OCH_3	31382-32-8	250–250.5	247–248[c]	17

[a] See ref 3. [b] *Anal.* Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.69; H, 7.70. [c] K. Friedrich and W. Hartmann, *Chem. Ber.*, **94**, 840 (1961).

The overall transformation can be rationalized by some scheme such as that shown in Scheme I. The

SCHEME I



first step is simply analogous to the overall reaction demonstrated in the earlier work. The product **4** in this case, however, contains an active methylene group which should undergo an aldol condensation with a second mole of aldehyde to form the corresponding triene.[4]

In order to test the validity of Scheme I, the quaternary salt **3** was treated with a single equivalent of base and tolualdehyde. The product was carefully worked up and chromatographed to afford a small amount of triene and a very polar gummy fraction. The mass spectrum (*m/e* 234.1175) and nmr (Ar H, 4 H at δ 7.2; vinyl protons 4 H δ 6–7; $ArCH_3$, 3 H at δ 2.3; PCH_3, 6 H, multiplets at δ 1.3 and 1.5) of the gum are in accord with a mixture of isomers of the intermediate **4**. Exposure of the gum to 1 equiv of potassium *tert*-butoxide and benzaldehyde gave the mixed triene, albeit in low yield (**6**, Ar = C_6H_5; Ar′ = *p*-$CH_3C_6H_4$), as the sole identifiable product. This then in broad outline provides evidence for the above scheme.

Experimental Section[5]

1-Methyl-3-phospholene Methiodide (3).—Methyldichlorophosphine (50 g) was added to a solution of 23 g of butadiene in

(4) See, for example, T. H. Kinstle and B. Mendanas, *Chem. Commun.*, 1699 (1968).
(5) Melting points are uncorrected and recorded as obtained on a Thomas-Hoover capillary melting point apparatus. Nmr spectra were determined in deuteriochloroform on a Varian A-60 spectrometer. The author is indebted to the Department of Physical and Analytical Chemistry of The Upjohn Co. for elemental and spectral determinations.

200 ml of hexane under N_2 in a drybox. At the end of 10 days, operating again in a drybox under nitrogen, the solid (33 g) was collected on a filter and transferred to a 1-l. three-necked flask. THF (400 ml) and Mg (6.5 g) were then added and the mixture (under N_2) was heated at reflux. 1,2-Dibromoethane (1 ml) was added and heating was continued for 16 hr. The mixture was allowed to cool and treated in turn with 40 ml of concentrated HCl and 30 ml of H_2O. The THF was then removed in vacuum, and the residue was made strongly basic and steam distilled. The distillate (250 ml) was extracted with ether.

The ether extract was dried over Na_2SO_4 and then treated with 10 ml of methyl iodide. At the end of 4 hr the precipitate was collected on a filter. One crystallization from acetonitrile–ether gave 10.15 g of solid, mp 287–290°.

Anal. Calcd for $C_6H_{12}IP$: C, 29.77; H, 5.00. Found: C, 29.87; H, 4.95.

Condensation Reaction.—In a typical run 2.36 g (0.01 mol) of the finely powdered methiodide **3** was added over 5 min to a mixture of 0.02 mol of the appropriate aldehyde and 2.24 g (0.02 mol) of *tert*-BuOK in 100 ml of THF. The mixture was stirred at room temperature for 5 hr and the solvent was then removed *in vacuo*. The residue was treated with H_2O and the precipitated gum recrystallized from an appropriate solvent.

1-Phenyl-6-(*p*-tolyl)-1,3,5-hexatriene (6).—To a well-stirred suspension of 4.72 g (0.02 mol) of the methiodide **3** and 2.40 g (0.02 mol) of tolualdehyde in 200 ml of THF there was added in portions 2.24 g (0.02 mol) of *tert*-BuOK. Following 1 hr of stirring at room temperature and 4 hr at reflux the solvent was removed *in vacuo*. The residue was treated with H_2O and Et_2O. There was obtained 0.20 g of crude symmetrical bistolyl triene, mp 220–230°. The gum obtained from the Et_2O layer was chromatographed on 300 ml of Florisil[6] (elution with 20% Me_2CO in Skellysolve B[7] followed by 100% Me_2CO); the last solvent brought over 0.80 g of **4** (Ar = *p*-$CH_3C_6H_4$) as a viscous gum.

A mixture of the above gum was allowed to react as above with 0.50 ml of benzaldehyde and 0.40 g of *tert*-BuOK in 25 ml of THF. The oily solid obtained on work-up was chromatographed on 100 ml of silica gel (elution with 5% Me_2CO in Skellysolve B). The solid fractions were combined and recrystallized from Skellysolve B to afford 70 mg of triene, mp 192.5–195°.[8]

Anal. Calcd for $C_{19}H_{18}$: C, 92.63; H, 7.37; mass spectrum (*m/e*) 246.1408. Found: C, 92.51; H, 7.34; mass spectrum (*m/e*) 246.1396.

Registry No.—**3**, 18005-44-2; **6**, 31382-34-0.

(6) A synthetic magnesia silica gel absorbent from the Floridin Co., Warren, Pa.

(7) A petroleum fraction, bp 60–70°, sold by the Skelly Oil Co.

(8) Lit. mp 195–196°: B. M. Mikhailov and L. S. Pardrov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 839 (1959).

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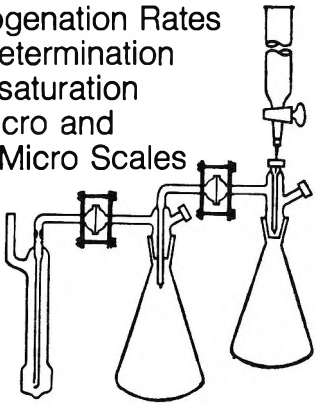

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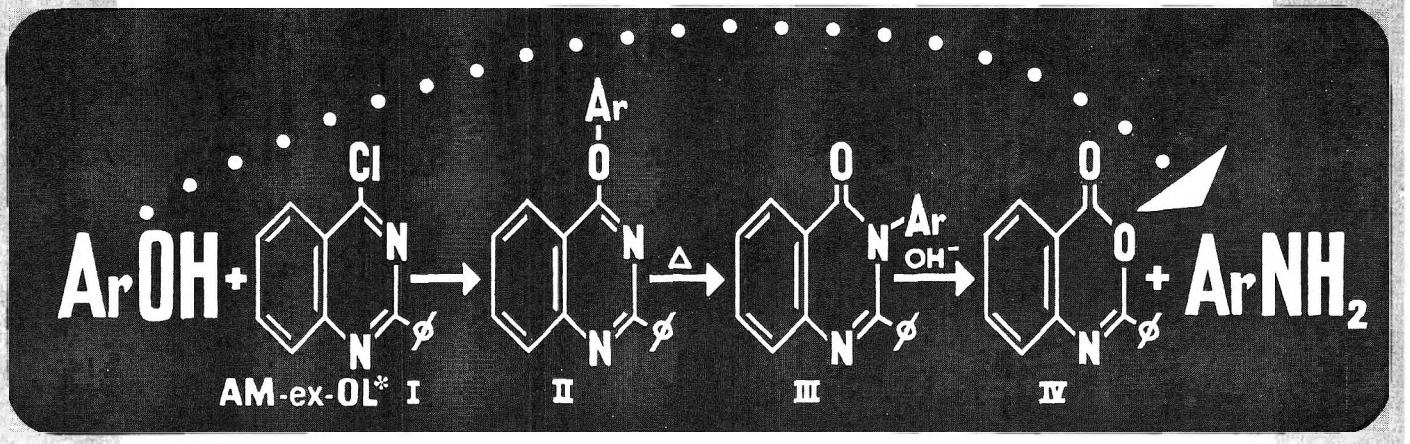

Overall yields are generally good; e.g. aniline from phenol 71%, 2,4-dichloroaniline and 2,3,6-trimethylaniline from the corresponding phenols 64 and 70% respectively. Even two steroidal phenols have been converted[2] to the amines in 67 and 58% yields.

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Heating this quinazoline under nitrogen at 325° for 130 minutes yielded 2, 3-diphenyl-4(3H)-quinazolinone III almost quantitatively. III need not be isolated. Thus, heating 16.3 g. of II in 30 ml. mineral oil under nitrogen for 4 hours at 325°, and then heating this mixture with a solution of 32 g. of KOH in 160 ml. ethylene glycol under nitrogen at 130° overnight, yielded on treatment with water, extraction with ether and treatment with HCl gas, 5.2 g. (76%) of aniline hydrochloride. The completion of the thermal rearrangement is best determined by IR or UV (II absorbs strongly at 259 mμ; III does not).

(1) a. R. A. Scherrer, Abstracts of Papers, 145th national meeting of the American Chemical Society, New York, N.Y., Sept. 1963, p. 33Q.
b. R. A. Scherrer and H. R. Beatty, J. Org. Chem., in preparation.

(2) a. D. F. Morrow and M. E. Butler, J. Org. Chem. 29, 1893 (1964).
b. D. F. Morrow and R. M. Hofer, J. Med. Chem., 9, 249 (1966).

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